# Decision Memo for Allogeneic Hematopoietic Stem Cell Transplantation (HSCT) for Myelodysplastic Syndrome (CAG-00415N)

# **Decision Summary**

CMS has determined that the evidence does not demonstrate that the use of allogeneic hematopoietic stem cell transplantation (HSCT) improves health outcomes in Medicare beneficiaries with myelodysplastic syndrome (MDS). Therefore, we determine that allogeneic HSCT for MDS is not reasonable and necessary under  $\S1862(a)(1)(A)$  of the Social Security Act (the Act). However, we believe the available evidence shows that allogeneic HSCT for MDS is reasonable and necessary under  $\S1862(a)(1)(E)$  of the Act through Coverage with Evidence Development (CED). Therefore, we are making the following decision.

Allogeneic HSCT for MDS is covered by Medicare only for beneficiaries with MDS participating in an approved clinical study that meets the criteria below.

A clinical study seeking Medicare payment for allogeneic hematopoietic stem cell transplantation for myelodysplastic syndrome pursuant to Coverage with Evidence Development (CED) must address one or more aspects of the following questions.

- 1. Prospectively, compared to Medicare beneficiaries with MDS who do not receive hematopoietic stem cell transplantation, do Medicare beneficiaries with MDS who receive hematopoietic stem cell transplantation have improved outcomes as indicated by:
  - o relapse free mortality,
  - o progression free survival,
  - relapse, and
  - overall survival?

- 2. Prospectively, in Medicare beneficiaries with MDS who receive hematopoietic stem cell transplantation, how do International Prognostic Scoring System (IPSS) score, patient age, cytopenias and comorbidities predict the following outcomes:
  - relapse free mortality,
  - progression free survival,
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- 3. Prospectively, in Medicare beneficiaries with MDS who receive hematopoietic stem cell transplantation, what treatment facility characteristics predict meaningful clinical improvement in the following outcomes:
  - relapse free mortality,
  - progression free survival,
  - relapse, and
  - overall survival?

The clinical study must adhere to the following standards of scientific integrity and relevance to the Medicare population:

- a. The principal purpose of the research study is to test whether a particular intervention potentially improves the participants' health outcomes.
- b. The research study is well supported by available scientific and medical information or it is intended to clarify or establish the health outcomes of interventions already in common clinical use.
- c. The research study does not unjustifiably duplicate existing studies.
- d. The research study design is appropriate to answer the research question being asked in the study.
- e. The research study is sponsored by an organization or individual capable of executing the proposed study successfully.
- f. The research study is in compliance with all applicable Federal regulations concerning the protection of human subjects found at 45 CFR Part 46. If a study is regulated by the Food and Drug Administration (FDA), it must be in compliance with 21 CFR parts 50 and 56.
- g. All aspects of the research study are conducted according to appropriate standards of scientific integrity (see http://www.icmje.org).
- h. The research study has a written protocol that clearly addresses, or incorporates by reference, the standards listed here as Medicare requirements for CED coverage.
- i. The clinical research study is not designed to exclusively test toxicity or disease pathophysiology in healthy individuals. Trials of all medical technologies measuring therapeutic outcomes as one of the objectives meet this standard only if the disease or condition being studied is life threatening as defined in 21 CFR § 312.81(a) and the patient has no other viable treatment options.
- j. The clinical research study is registered on the ClinicalTrials.gov website by the principal sponsor/investigator prior to the enrollment of the first study subject.

- k. The research study protocol specifies the method and timing of public release of all prespecified outcomes to be measured including release of outcomes if outcomes are negative or study is terminated early. The results must be made public within 24 months of the end of data collection. If a report is planned to be published in a peer reviewed journal, then that initial release may be an abstract that meets the requirements of the International Committee of Medical Journal Editors
  - (http://www.icmje.org). However a full report of the outcomes must be made public no later than three (3) years after the end of data collection.
- I. The research study protocol must explicitly discuss subpopulations affected by the treatment under investigation, particularly traditionally underrepresented groups in clinical studies, how the inclusion and exclusion criteria effect enrollment of these populations, and a plan for the retention and reporting of said populations on the trial. If the inclusion and exclusion criteria are expected to have a negative effect on the recruitment or retention of underrepresented populations, the protocol must discuss why these criteria are necessary.
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Consistent with section 1142 of the Social Security Act, AHRQ supports clinical research studies that CMS determines meet the above-listed standards and address the above-listed research questions.

Revisions to sections 110.8.1 of the NCD Manual are available in Appendix C.

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# **Decision Memo**

TO: Administrative File: (CAG-00415N)

Allogeneic Hematopoietic Stem Cell Transplantation for Myelodysplastic Syndrome

FROM:

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SUBJECT: Decision Memorandum for Allogeneic Hematopoietic Stem Cell Transplantation for Myelodysplastic Syndrome

DATE: August 4, 2010

### I. Decision

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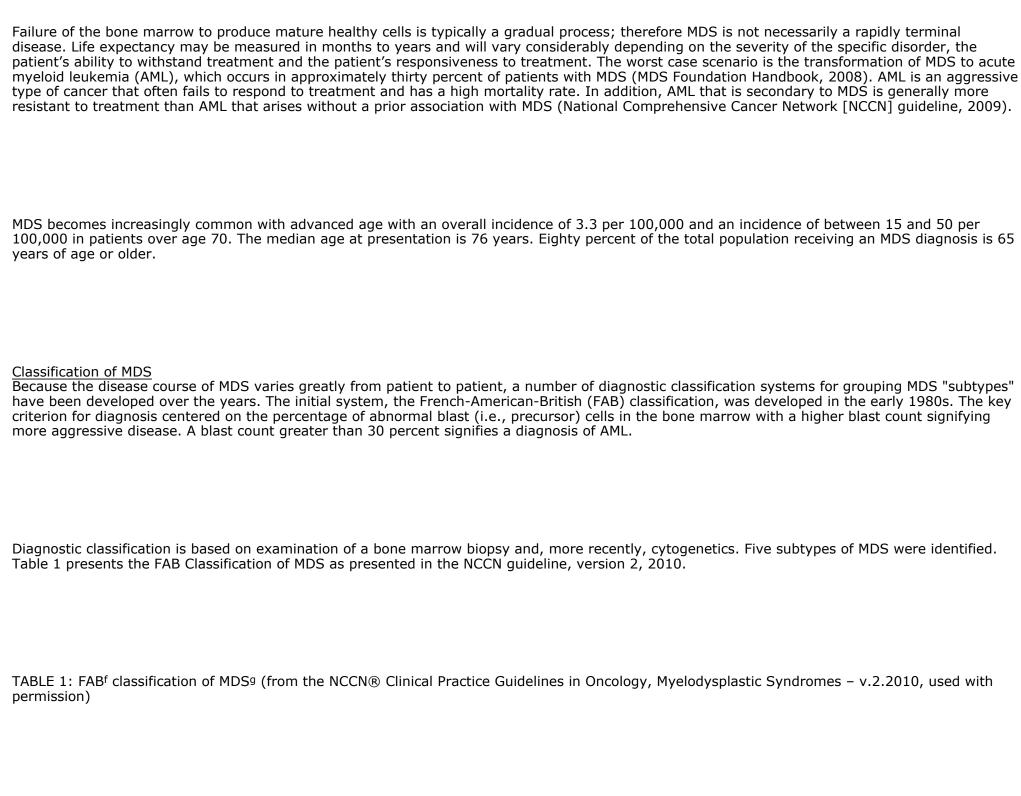
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Consistent with section 1142 of the Social Security Act, AHRQ supports clinical research studies that CMS determines meet the above-listed standards and address the above-listed research questions.

Revisions to sections 110.8.1 of the NCD Manual are available in Appendix C.
II. Background
Myelodysplastic Syndrome (MDS) refers to a group of diverse blood disorders in which the bone marrow does not produce enough healthy, functioning blood cells. These disorders are varied with regard to clinical characteristics, cytologic and pathologic features, and cytogenetics.
Clinical Background and Burden of Disease There are three "families" of cells commonly found in the blood: red cells, white cells, and platelets. The abnormal production of blood cells in the bone marrow leads to low blood cell counts, referred to as cytopenia, which are a hallmark feature of MDS along with a dysplastic and hypercellular-appearing bone marrow. Most patients present with signs or symptoms of anemia (due to abnormally lowered red cell counts), which can be accompanied by infection (due to abnormally low white cell counts) and/or bleeding (due to abnormally low platelet counts). A persistently low blood cell count can necessitate the administration of frequent transfusions that over time may also have a decreasing positive impact for the patient, which is referred to as refractory cytopenia with transfusion dependency. Although some patients may not have any symptoms, most patients with MDS ultimately die from their low blood counts according to Nimer (2008).



FAB subtype	% Peripheral blasts	% Bone marrow blasts
Refractory anemia (RA)	< 1	< 5
Refractory anemia with ringed sideroblasts (RARS)	< 1	< 5
Refractory anemia with excess blasts (RAEB)	< 5	5-20
Refractory anemia with excess blasts in transformation (RAEB -t)	<u>≥</u> 5	21-30
Chronic myelomonocytic leukemia (CMML) (> 1,000 monocytes/mcL blood)	< 5	5-20

f FAB = French-American-British
g Bennett JM, Catovsky D, Daniel MT, et al. Proposals for the classification of the myelodysplastic syndromes. Br J Haematol. 1982; 51:189-199.
h WHO = World Health Organization

In 2001, the World Health Organization (WHO) expanded upon the FAB system by taking into account the number of types of abnormal "families" of blood cells, the presence or absence of certain cytogenetics abnormalities as well as by lowering the maximum allowable percentage of blast cells in the blood (Nimer, 2008). The WHO classification system was further updated in 2008 in order to incorporate new scientific and clinical information and to add new diseases (NCCN guideline, 2009). The maximum blast count required for AML was reduced to twenty percent. Table 2 presents the 2008 WHO Classification of MDS as presented in the NCCN guidelines.

TABLE 2: Classification Systems for de novo MDS: 2008 WHO<sup>h</sup> Classification of MDS<sup>i</sup> (from the NCCN® Clinical Practice Guidelines in Oncology, Myelodysplastic Syndromes – v.2.2010, used with permission)

Subtype	Blood	Bone marrow
Refractory cytopenia with unilineage dysplasia (RCUD) <sup>j</sup>	Single or bicytopenia	Dysplasia in > 10 % of one cell line, < 5% blasts
Refractory anemia with ring sideroblasts (RARS)	Anemia, no blasts	≥15 % of erythroid precursors w/ring sideroblasts, erythroid dysplasia only, < 5 % blasts
Refractory cytopenia with multilineage dysplasia (RCMD)	Cytopenia(s): < 1 x 10 9/L monocytes	Dysplasia in $\geq$ 10 % of cells in $\geq$ 2 hematopoietic lineages, $\pm$ 15 % ring sideroblasts, < 5 % blasts;
Refractory anemia with excess blasts-1 (RAEB-1)	Cytopenia(s): ≤ 2-4 % blasts, < 1 x 10 9/L monocytes	Unilineage or multilineage dysplasia, No Auer rods, 5 % to 9 % blasts

Subtype	Blood	Bone marrow
Refractory anemia with excess blasts-2 (RAEB-2)	Cytopenia(s): 5-19 % blasts, < 1 x 10 9/L monocytes	Unilineage or multilineage dysplasia Auer rods ±, 10 % to 19 % blasts
Myelodysplastic syndrome, unclassified (MDS-U)	Cytopenias	Unilineage dysplasia or no dysplasia but characteristic MDS cytogenetics, < 5% blasts
MDS associated with isolated del(5q)	Anemia, platelets normal or increased	Unilineage erythroid dysplasia, isolated del 5(q), < 5 % blasts

Brunning R, Orazi A, Germing U, et al. Myelodysplastic Syndromes, Chapter 5, in Swerdlow S, Campo E, Harris NL, et al. World Health Organization Classification of Tumours of Haematopoietic and Lymphoid Tissue, 4th edition. IARC Press, 2008, p88-103.

TABLE 3: Classification Systems for de novo MDS: Myelodysplastic/Myeloproliferative Neoplasms (MDS/MPN) WHO Classification<sup>k</sup> (from the NCCN® Clinical Practice Guidelines in Oncology, Myelodysplastic Syndromes – v.2.2010, used with permission)

Subtype	Blood	Marrow
Chronic myelomonocytic leukemia-1 (CMML-1)	> 1x109/L monocytes, <5% blasts	Dysplasia in 1 hematopoietic line, <10% blasts
CMML-2	> 1x109/L monocytes, 5-19% blasts or Auer rods	Dysplasia in 1 hematopoietic line, 10-19% blasts or Auer rods
Atypical chronic myeloid leukemia (CML), Bcr-Abl 1 negative	WBC 13x109/L, neutrophil precursors >10%, < 20% blasts	Hypercellular, <20% blasts
Juvenile myelomonocytic leukemia (JMML)	> 1x109/L monocytes, < 20% blasts <sup>l</sup>	>1x10 <sup>9</sup> /L monocytes, <20% blastsl
	Dysplasia + myeloproliferative featuresm , No prior MDS or MPN	Dysplasia + myeloproliferative features

Acute myeloid leukemia with myelodysplasia-related changes<sup>n</sup> WHO Classification<sup>o</sup>

<sup>&</sup>lt;sup>j</sup> This category encompasses refractory anemia (RA), Refractory Neutropenia (RN) and Refractory thrombocytopenia (RT). Cases of RN and RT were previously classified as MDS Unclassified.

- AML post MDS or MDS/MPN
- 2. AML with an MDS-related cytogenetic abnormality
- 3. AML with multilineage dysplasia

<sup>k</sup> Orazi A, Bennet JM, Germing U, et al, Myelodysplastic/Myeloproliferative Neoplasms, Chapter 4, in Swerdlow S, Campo E, Harris NL, et al. (Eds.). World Health Organization Classification of Tumours of Haematopoietic and Lymphoid Tissues, 4th edition. IARC Press, 2008, pp 76-86.

- Ph negative plus 2 features: Hb F, PB immature myeloid cells, WBC  $>10\times109$ /L, clonal chromosomal abnormality, GM-CSF hypersensitivity in vitro, for example, thrombocytosis, leukocytosis, splenomegaly.
- <sup>n</sup> Greater than 20% blasts in PB or marrow. Some cases with 20-29% blasts, especially if arising from MDS, may be slowly progressive and may behave more similar to MDS (RAEB-t by FAB classification) than to overt AML.
- o Arber DA, Brunning RD, Orazi A, et al. Acute myeloid leukaemia with myelodysplasia-related changes, In Chapter 6, Acute Myeloid Leukemia and Related Precursor Neoplasms, in Swerdlow S, Campo E, Harris NL, et al. (Eds.). World Health Organization Classification of Tumours of Haematopoietic and Lymphoid Tissues, 4th edition. IARC Press, 2008, pp 124-126.

Although the revisions to the FAB system and hence the resultant WHO diagnostic classification system are considered to be an improvement, the 2009 NCCN guideline states that "the NCCN MDS panel members currently endorse reporting and using both the FAB and the WHO classification systems" in clinical practice. Similarly, when evaluating clinical studies and comparing results across those studies it is important to note whether patients were diagnosed with the FAB or WHO classification system.

Due to the highly variable nature of the patient population with regards to MDS subtype, severity of disease and baseline medical condition, the clinical management of a patient with MDS is highly individualized and can range from solely supportive care with periodic transfusions and antibiotics to intensive chemotherapy with or without transplantation. The International Prognostic Scoring System (IPSS) is the classification scheme widely recognized and used in determining the most suitable treatment regimen.

The IPSS scheme, as first described in Greenberg, et al. (1998), is the worldwide system used for risk-based grading of the severity and progression of MDS and for ascertaining the patient's prognosis. The goal of the IPSS is to determine, for a given MDS subtype, the patient's chance for survival and the risk for MDS to transform (i.e., progress) to AML (NCCN guideline, 2009). The authors found that three major variables (marrow blast percentage, number of cytopenias and cytogenetics subgroup) could determine the outcome; a risk score was assigned to each. Four risk groups with regards to survival and progression to AML were then created by combining the risk scores for the three major variables.

Table 4 presents the IPSS Classification system as presented in the 2009 NCCN guideline.

TABLE 4: IPSS (IPSS p,q) Classification System (from the NCCN® Clinical Practice Guidelines in Oncology, Myelodysplastic Syndromes – v.2.2010, used with permission).

		Survival and AML evolution Score value				
Prognostic variable	0	0.5	1.0	1.5	2.0	
Marrow blasts (%)r	< 5	5-10	-	11-20	21-30	
Karyotypes	Good	Intermediate	Poor			
Cytopenia <sup>t</sup>	0/1	2/3				

Risk category (% IPSS pop.)	Overall score	Median survival (y) in the absence of therapy	25% AML progression (y) in the absence of therapy
LOW (33)	0	5.7	9.4
INT-1 (38)	0.5-1.0	3.5	3.3
INT-2 (22)	1.5-2.0	1.1	1.1
HIGH (7)	≥ 2.5	0.4	0.2

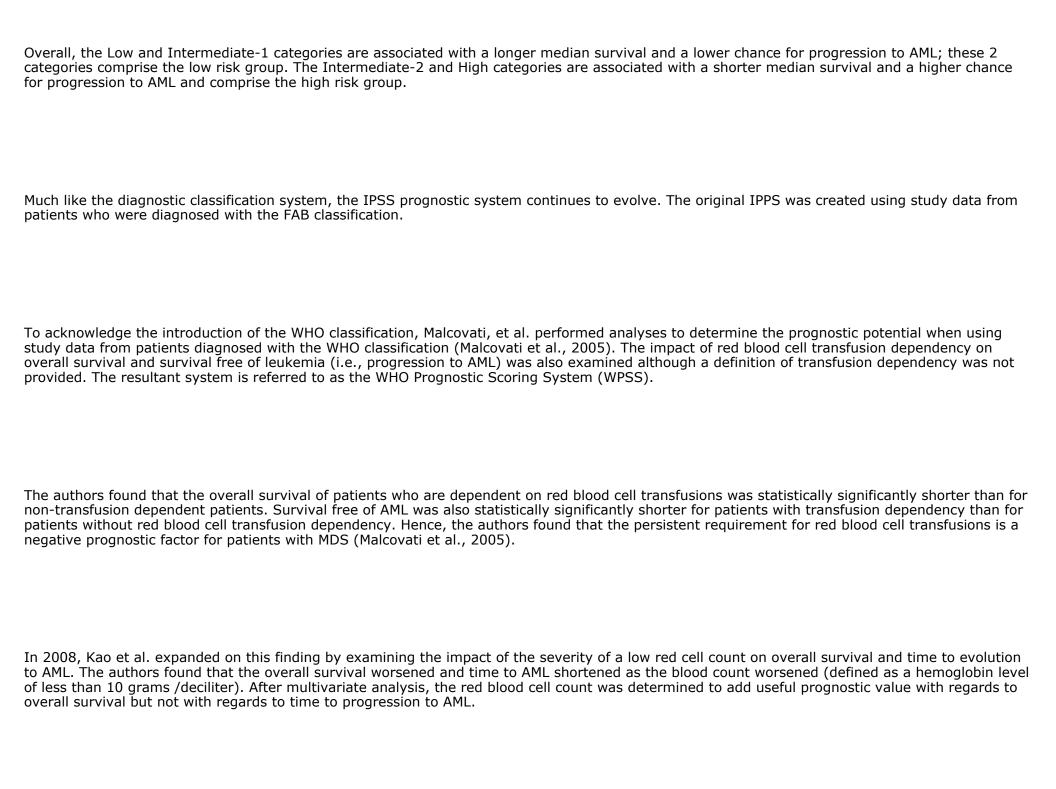
p IPSS = International Prognostic Scoring System.

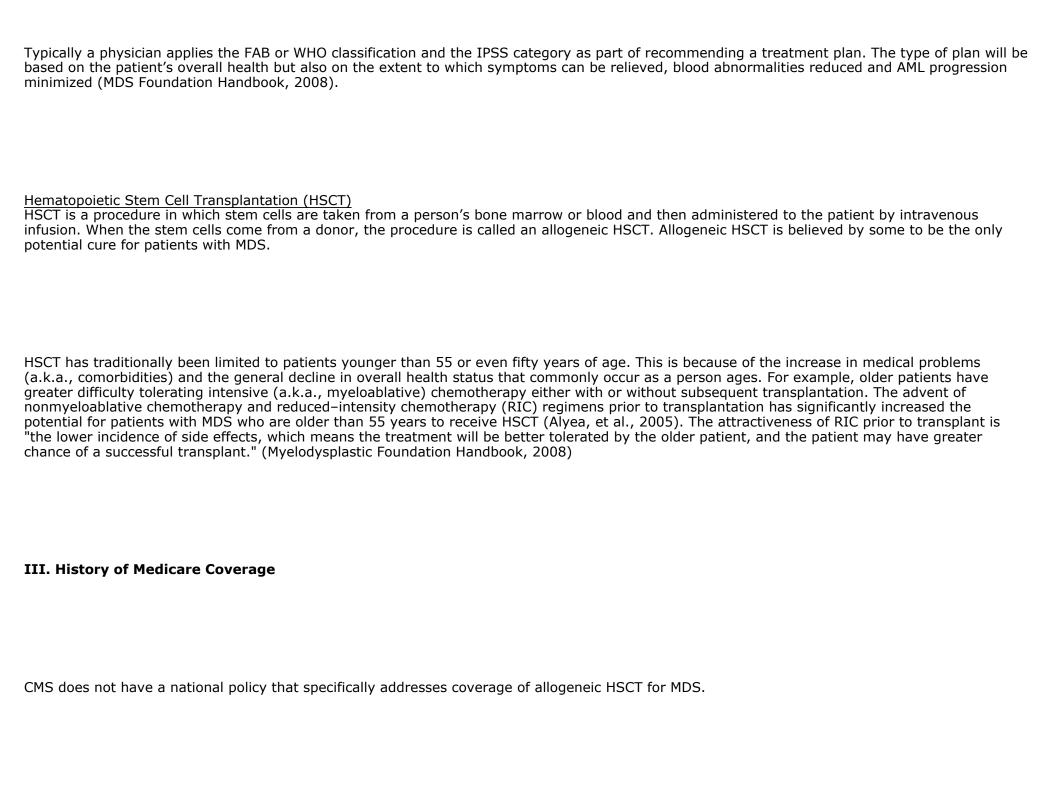
Tables 1-4 are reproduced with permission from the NCCN 2.2010 Myelodysplastic Syndromes Clinical Practice Guidelines in Oncology, ©National Comprehensive Cancer Network, 2010. Available at: <a href="http://www.nccn.org">http://www.nccn.org</a> (accessed February 23, 2010).

q This research was originally published in Blood. Greenberg P, Cox C, LeBeau M, et al. International scoring system for evaluating prognosis in myelodysplastic syndromes. Blood 1997;89:2079-2088; Erratum. Blood 1998;91:1100. © The American Society of Hematology.

r Patients with 20-30 % blasts may be considered as MDS or AML.

s Cytogenetics: Good = normal, -Y alone, del (5q) alone, del (20q) alone; Poor = complex (3 abnormalities) or chromosome 7 anomalies; Intermediate = other abnormalities. [This excludes karyotypes t (8; 21), inv16, and t (15; 17), which are considered to be AML not MDS.] t Cytopenias: neutrophil count <1,800/mcL, platelets < 100,000/mcL, Hb < 10q/dL.





Section 110.8.1 of the National Coverage Determination (NCD) Manual
constitutional of the Hadishar coverage Determination (NGD) Handar
(http://www.cms.gov/manuals/103_cov_determ/ncd103c1_Part2.pdf) governs national coverage and noncoverage of Stem Cell Transplants, as described below.
Indications and Limitations of Coverage
Allogeneic Stem Cell Transplantation
Allogeneic stem cell transplantation is a procedure in which a portion of a healthy donor's stem cell or bone marrow is obtained and prepared for intravenous infusion.

#### **Covered Indications**

The following uses of allogeneic bone marrow transplantation are covered under Medicare:

- Effective for services performed on or after August 1, 1978, for the treatment of leukemia, leukemia in remission, or aplastic anemia when it is reasonable and necessary; and
- Effective for services performed on or after June 3, 1985, for the treatment of severe combined immunodeficiency disease (SCID), and for the treatment of Wiskott-Aldrich syndrome.

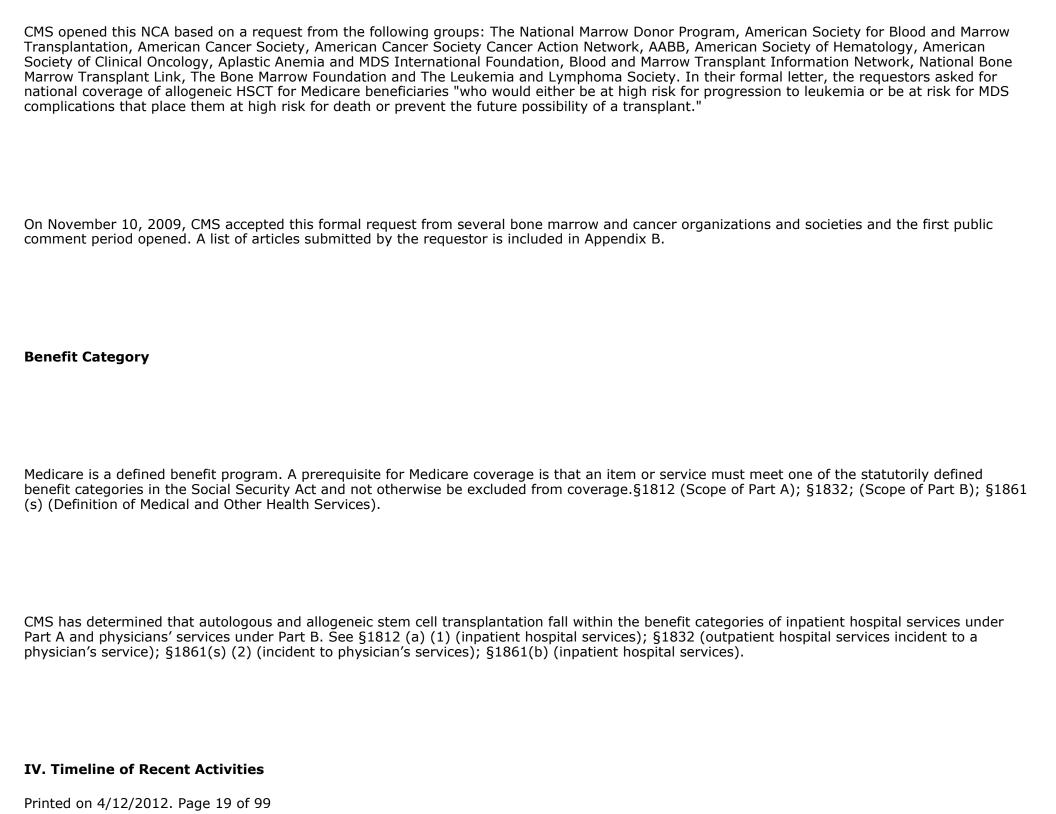
b.

### Noncovered Indications

Effective for services performed on or after May 24, 1996, allogeneic stem cell transplantation is not covered as treatment for multiple myeloma.

In the absence of a national coverage determination, contractors have the discretion to determine coverage for allogeneic HSCT for all other indications through the local coverage determination (LCD) process or by individual claim by claim adjudication.

## **Current request**



November CMS accepts formal NCD request for coverage of the allogeneic hematopoietic stem cell transplantation for myelodysplastic syndrome. 10, 2009 The tracking sheet is posted and the initial 30-day comment period begins.

December Initial 30 day public comment period closes. Comments are posted on the website. 10, 2009

May 6, CMS posts the proposed decision memorandum for 30 days of public comment period. 2010

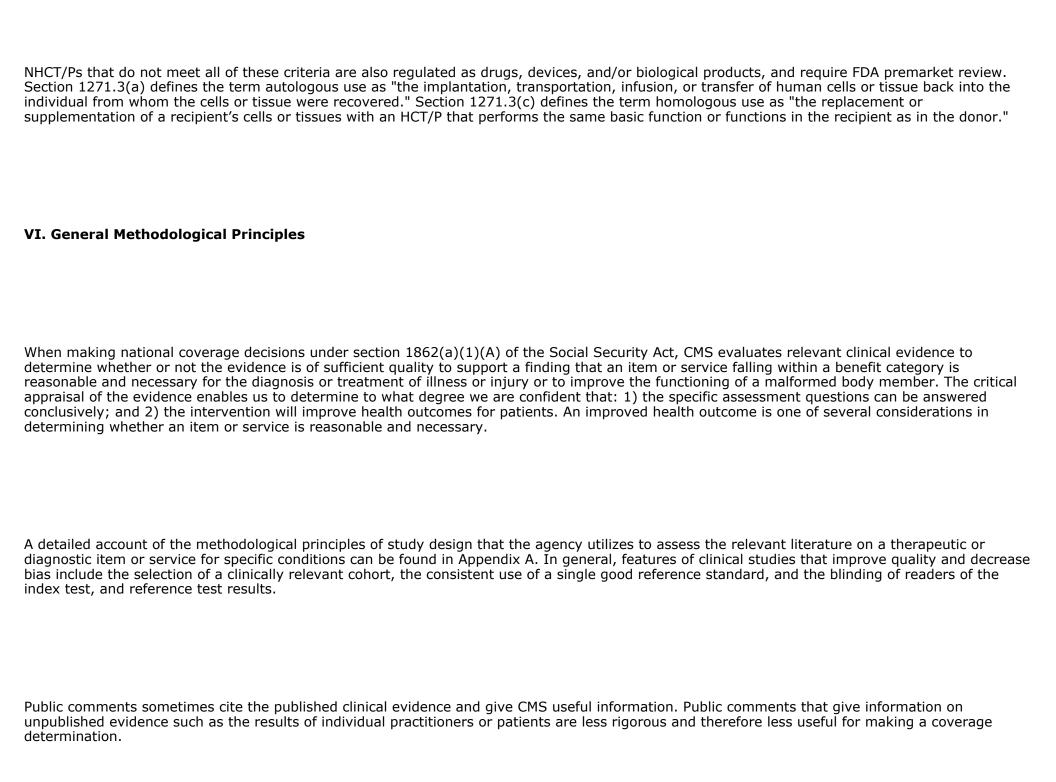
June 5, The public comment period on the proposed decision memo closes with 14 public comments received. 2010

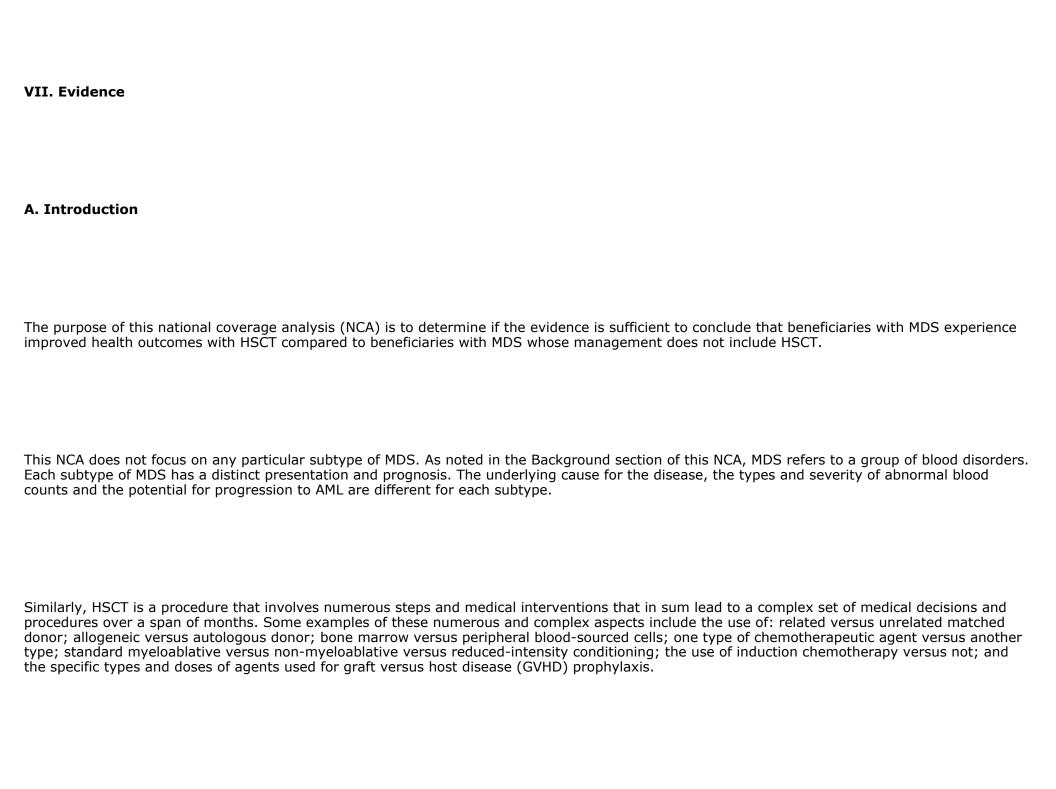
#### V. FDA Status

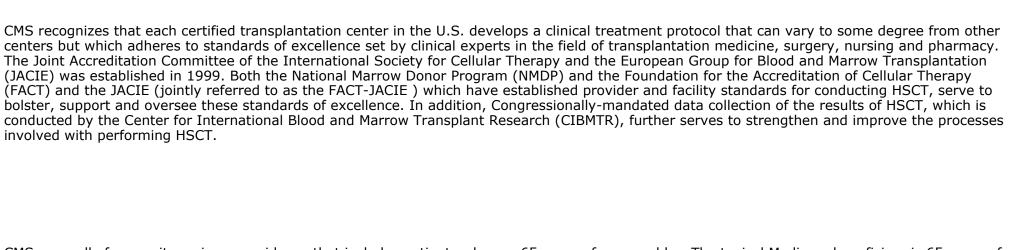
Hematopoietic stem/progenitor cells (HPC) for transplantation are regulated as human cells, tissues, and cellular-and tissue based products (HCT/Ps) by FDA under 21 CFR. §1271. Section 1271.3(d) defines human cells, tissues, or cellular or tissue-based products (HCT/Ps) as "articles containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion or transfer into a human recipient. Examples of HCT/Ps include, but are not limited to, bone, ligament, skin, dura mater, heart valve, cornea, hematopoietic stem cells derived from peripheral and cord blood, manipulated autologous chondrocytes, epithelial cells on a synthetic matrix, and semen or other reproductive tissue."

The regulatory approach to HCT/Ps, including HPC, distinguishes among autologous products, allogeneic products from first- or second-degree relatives, and allogeneic products form unrelated donors. HCT/Ps that meet all of the criteria set forth in 21 CFR §1271.10(a) are regulated solely under section 361 of the PHS Act and the regulations in Part 1271, and no FDA premarket review is required. To satisfy these criteria, a HCT/P must:

- be minimally manipulated;
- be intended for homologous use only;
- not be combined with another article (with some limited exceptions); and not have a systemic or metabolic effect;
- or if it does, it must be intended for autologous use or use by a first- or second-degree blood relative.





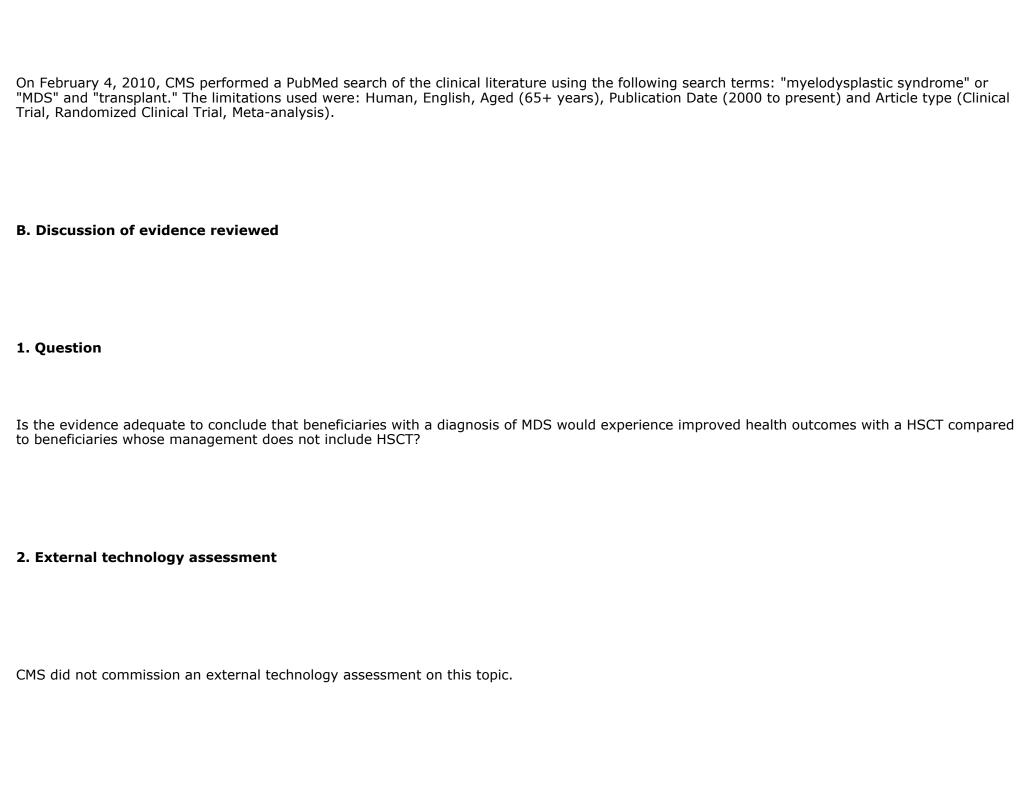


CMS generally focuses its review on evidence that includes patients who are 65 years of age or older. The typical Medicare beneficiary is 65 years of age or older; however, a relatively small percentage of beneficiaries may be younger than 65 year old due to Medicare entitlement based on other factors such as end stage renal disease or disability.

However, CMS acknowledges that traditionally HSCT was routinely contraindicated in patients with MDS who were older than 55 or even 50 years of age due to the patient's inability to tolerate the standard myeloablative conditioning regimen. The literature, therefore, is still dominated by evidence generated in patients younger than 65 years of age. This is slowly changing with the relatively recent introduction of non-myeloablative conditioning (NMA) and reduced-intensity conditioning (RIC) regimens for patients with MDS who are older than 65 years or who have other contra-indications to HSCT.

There is considerable morbidity and mortality associated with some subtypes of MDS as well as with HSCT. The greater chance for non relapse mortality (NRM) or transplant-related mortality (TRM) with the use of standard myeloablative conditioning prior to transplantation has traditionally limited transplantation to nonelderly and nondebilitated patients (Martino, et al., 2006). Thus, the primary outcomes of interest in this NCA are overall survival (OS), progression-free survival (PFS) and TRM or NRM.

#### **Literature Search**



3. Internal technology assessment
Results from the CMS literature search as well as the literature articles submitted by the requestors and the literature references provided by public commenters were considered for the internal technology assessment (TA). The CIBMTR Progress Report for calendar year 2008 was reviewed to find a listing of published articles based on research performed on the CIBMTR database. In addition, an Internet search was performed to identify any available evidence-based guidelines and professional society position statements.
From the above evidence sources, CMS looked for published, peer-reviewed full articles (i.e., not abstracts) of controlled clinical trials that provided results on the use of HSCT versus other therapies in the clinical management of patients with MDS of any subtype. Emphasis was placed on articles that presented evidence in the Medicare population (i.e., 65 years of age or older).
Articles that provided background information on MDS (e.g., epidemiology), a study that did not investigate HSCT (e.g., a study that examined the safety and/or efficacy of a chemotherapeutic agent) or a non-clinical study (i.e., animal research) were not included in this internal technology assessment
4. Evidence Summary
Cutler CS, et al. A decision analysis of allogeneic bone marrow transplantation for the myelodysplastic syndromes: Delayed transplantation for low-risk myelodysplasia is associated with improved outcome. Blood2004; 104:579-585.

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The authors performed a decision analysis to investigate the optimal timing for bone marrow transplantation for patients with MDS. There were two MDS data sources for the analysis: the International MDS Risk Analysis Workshop (IMRAW) database was the source for the nontransplantation cohort ( $n=184$ ); the International Bone Marrow Transplant Registry (IBMTR; $n=193$ )) and the Fred Hutchinson Cancer Research Center ( $n=67$ ) databases were the sources for the MDS transplantation cohort. IBMTR was the one AML data source ( $n=230$ ). All patients had received myeloablative conditioning.
Three possible transplantation strategies were tested using a Markov decision model: 1) transplantation at time of MDS diagnosis; 2) transplantation at time of progression to AML; 3) transplantation at a fixed time interval after diagnosis. Analyses were performed for all four IPSS risk groups. A base case was used consisting of a 35 year old man with newly diagnosed MDS and an available HLA-matched sibling donor.
All patients were sixty years old or younger. The median age in the nontransplantation cohort was 49.8 years while the median age in the various transplant groups was 39.4 to 45.6 years. In the nontransplantation group, the majority (73.9%) had an IPSS Low or Intermediate-1 risk profile. In the transplantation group, the majority (75%) had an IPSS Intermediate-1 or Intermediate-2 profile.
The outcomes results are reported in tables 5-8 below.
TABLE 5: Median survival in months according to transplantation status (from Cutler, et al., 2004).

	<b>Nontransplantation Cohort</b>	<b>Transplantation Cohort</b>
Median Survival (months)	62.9	14
Significance not stated		

TABLE 6: Median survival in months and 25% AML transformation time by IPSS risk group for the nontransplantation cohort (from Cutler, et al., 2004).

IPSS	Low	Intermediate-1	Intermediate-2	High
Median Survival (months)	141.1	62.9	22.5	4.9
25 % AML transformation time		84.6	19.2	2.7
All differences P< 0.001				

TABLE 7: Median survival in months according to IPSS risk group for the transplantation cohort (from Cutler, et al., 2004).

IPSS	Low	Intermediate-1	Intermediate-2	High
Median Survival (months)	40.2	20.5	14.8	6.1
All differences P = 0.04				

TABLE 8: Discounted life expectancy, in years, for alternative transplantation strategies (from Cutler, et al., 2004).

Discounted life expectancy (yrs)					
Transplantation at diagnosis	Transpla	ntation at	a fixed t	ime point	Transplantation at AML progression
	2 yr	4 yr	6 yr	8 yr	
6.51	6.86	7.47	7.46	7.49*	7.21
4.61	4.74	4.72	5.02	5.20*	5.16
	6.51	Transplantation at diagnosis Transpla 2 yr 6.51 6.86	Transplantation at diagnosis Transplantation at 2 yr 4 yr 6.51 6.86 7.47	Transplantation at diagnosis Transplantation at a fixed to 2 yr 4 yr 6 yr 6.51 6.86 7.47 7.46	Transplantation at diagnosis Transplantation at a fixed time point  2 yr 4 yr 6 yr 8 yr  6.51 6.86 7.47 7.46 7.49*

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	Discounted life expectancy (yrs)						
Intermediate-2	4.93*	3.21	2.94	2.85	2.84	2.84	
High	3.20*	2.75	2.75	2.75	2.75	2.75	
* Dominant stra	ategies						

The authors concluded that "delayed transplantation for IPSS Low and Intermediate-1 risk groups is associated with maximum discounted life years" while for the IPSS Intermediate-2 and High risk groups "transplantation at the time of diagnosis is associated with maximization of discounted life years." They also hypothesized that for the IPSS Low and Intermediate-1 risk groups the optimal timing of transplantation "is at the time of the development of a new cytogenetics abnormality, the appearance of a clinically important cytopenia, or the progression from one IPSS group to a higher risk group."

Martino R, et al. Retrospective comparison of reduced-intensity conditioning and conventional high-dose conditioning for allogeneic hematopoietic stem cell transplantation using HLA-identical sibling donors in myelodysplastic syndromes. Blood2006; 108:836-846.

A retrospective, multicenter study was performed to evaluate myeloablative conditioning versus reduced-intensity conditioning (RIC) prior to HSCT in patients with MDS or AML. Disease relapse, progression-free survival, overall survival and nonrelapse mortality were among the outcomes studied.

Myeloablative conditioning was administered to 621 patients with MDS while 215 patients with MDS received RIC. Sixty-three percent of the patients who received myeloablative conditioning had MDS while 59% of the patients who received RIC had MDS. Of the fifty percent of patients for whom the authors could collect IPSS-related information, 66% who received myeloablative conditioning had high risk MDS and 69% who received RIC had high risk MDS. Twenty-seven percent of patients who received myeloablative conditioning were older than 50 years and 73% of the patients who received RIC were older than 50 years.

The outcomes results are reported in tables 9-12. After each table is a report of the results of a multivariate analysis for that outcome.

TABLE 9: Incidence of nonrelapse mortality (from Martino, et al., 2006).

	Myeloablative	RIC
% Nonrelapse mortality (95% CI)		
3-month	0.20 (0.17-0.23)	0.15 (0.11-0.21)
1-year	0.28 (0.25-0.32)	0.20 (0.15-0.26)
3-year	0.32 (0.28-0.36)	0.22 (0.17-0.28)
P = 0.04		

Multivariate analysis of 3-year nonrelapse mortality showed that the use of RIC reduced nonrelapse mortality (HR, 0.61, 95%CI, 0.41-0.91; p = 0.015) compared to myeloablative conditioning and that patient age older than fifty years increased the nonrelapse mortality compared to patient age fifty and younger (HR, 1.4, 95%CI, 1.1-1.8; p = 0.04).

TABLE 10: Incidence of disease progression/relapse (from Martino, et al., 2006).

Myeloablative	RIC
0.08 (0.06-0.10)	0.14 (0.11-0.20)
0.22 (0.19-0.25)	0.35 (0.30-0.43)
0.27 (0.24-0.31)	0.45 (0.38-0.53)
	0.08 (0.06-0.10) 0.22 (0.19-0.25)

	Myeloablative	RIC
P < 0.01		

Multivariate analysis of 3-year disease progression/relapse showed that the use of RIC increased disease progression/relapse (HR, 1.64, 95% CI, 1.2 -2.2; p = 0.001) compared to myeloablative conditioning; and that an advanced stage of disease increased disease progression/relapse compared to an early stage of disease (HR, 2.2, 95% CI, 1.2-4.1; P = 0.01).

TABLE 11: Incidence of progression-free survival (from Martino, et al., 2006).

	Myeloablative	RIC
% Progression-free survival (95% CI)		
3-month	0.72 (0.74-0.80)	0.76 (0.69-0.81)
1-year	0.50 (0.46-0.54)	0.45 (0.38-0.52)

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	Myeloablative	RIC
3-year	0.41 (0.37-0.45)	0.33 (0.27-0.40)
P = 0.1		

Multivariate analysis of 3-year progression-free survival showed that the use of RIC did not impact the progression-free survival compared to myeloablative conditioning; and that a diagnosis of MDS increased the progression-free survival compared to a diagnosis of secondary AML (HR, 0.78, 95% CI, 0.6-0.98; p = 0.03). There was a trend toward a decrease in progression-free survival in patients older than fifty years compared to patients fifty years or younger.

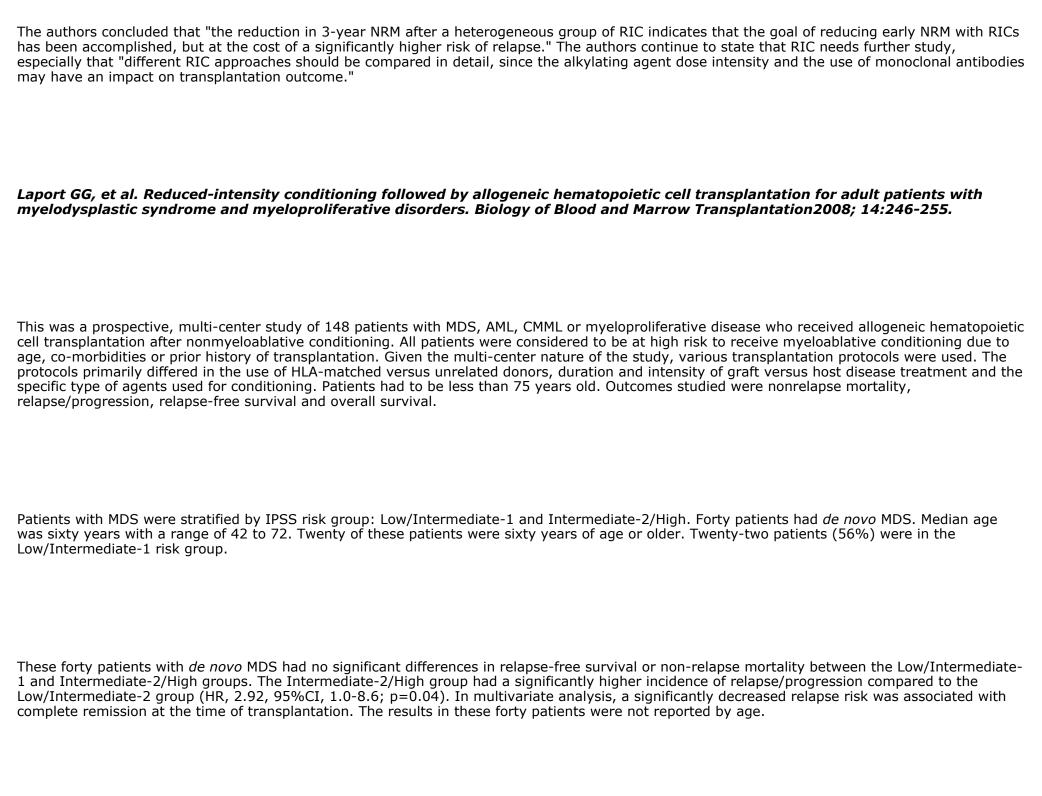
TABLE 12: Overall survival (from Martino, et al., 2006).

	Myeloablative	RIC
% Overall survival (95% CI)		

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	Myeloablative	RIC
3-month	0.82 (0.79-0.85)	0.84 (0.79-0.89)
1-year	0.58 (0.54-0.62)	0.57 (0.49-0.63)
3-year	0.45 (0.41-0.49)	0.41 (0.35-0.47)
P = 0.7		

Multivariate analysis of 3-year overall survival showed that the use of RIC did not impact overall survival compared to myeloablative conditioning; that patient age older than fifty years decreased the overall survival compared to patient age fifty and younger (HR, 1.3, 95% CI, 1.05-1.6); p = 0.02); and that a diagnosis of MDS increased overall survival compared to a diagnosis of secondary AML (HR, 0.72, 95% CI, 0.57-0.92; p = 0.007).



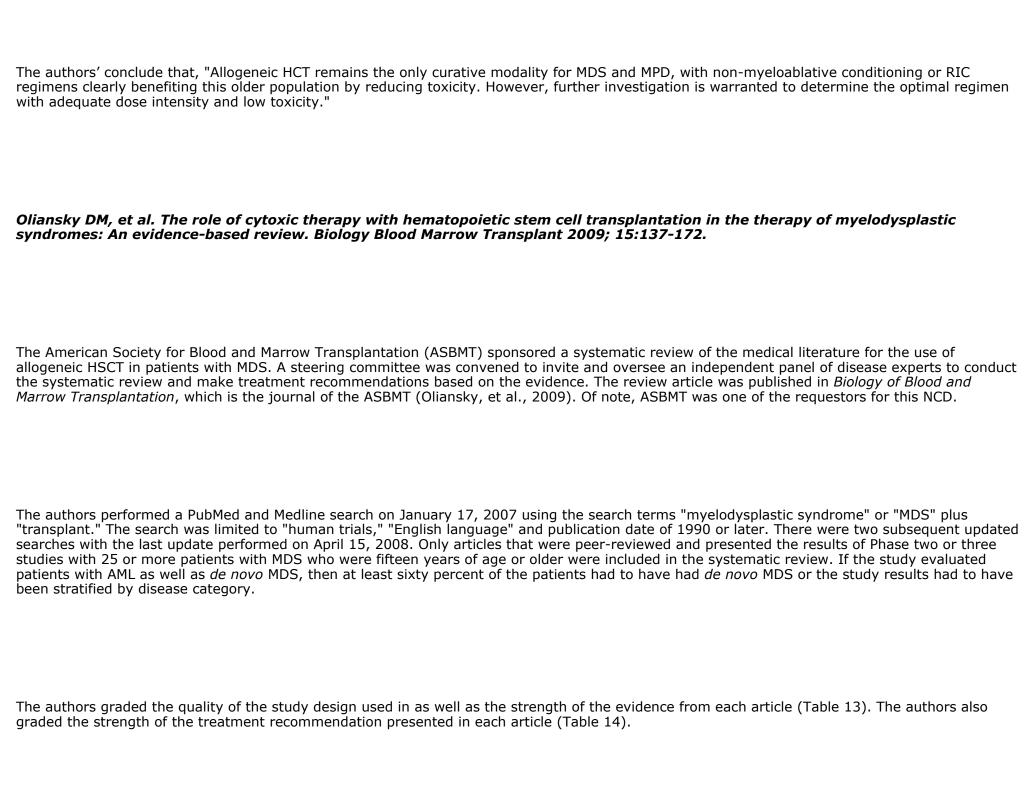
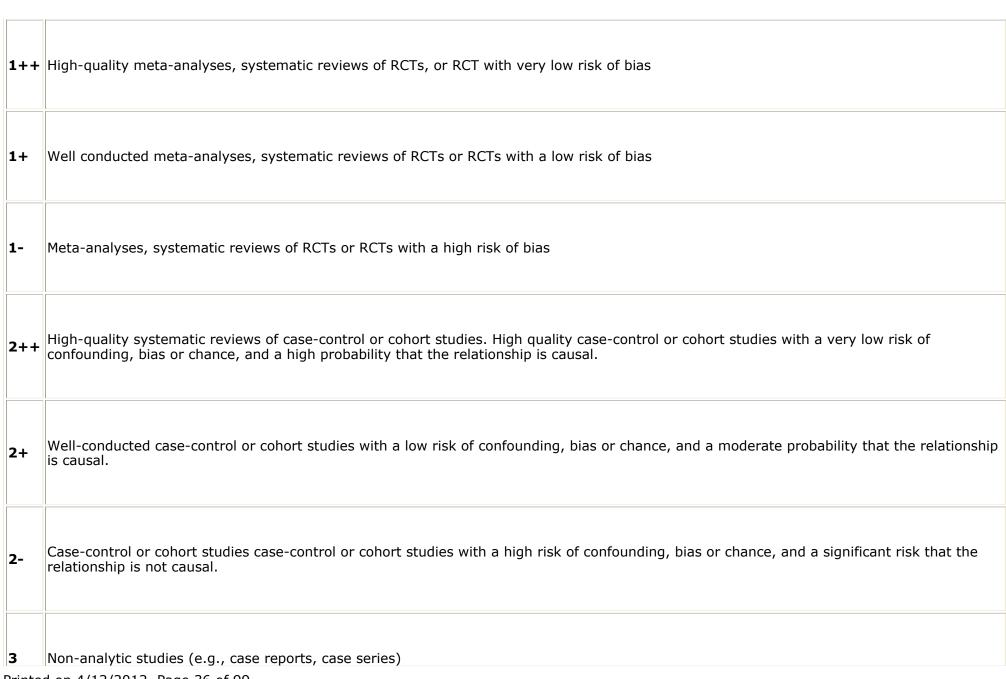


TABLE 13: Grading the Quality of Study Design and the Strength of the Evidence (from Oliansky, et al., 2009).



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Expert opinion
CT= randomized controlled trial
BLE 14: Grading the Strength of the Treatment Recommendation (from Oliansky, et al., 2009).
ble 14. Grading the Strength of the Fredthent Recommendation (nom Onarisky, et al., 2003).
At least one meta-analysis, systematic review or RCT rated as 1++ and directly applicable to the target population; or a systematic review of RCTs or a body of evidence consisting principally of studies rated as 1+, directly applicable to the target population and demonstrating overall consistency of results
A body of evidence including studies rated as 2++ directly applicable to the target population and demonstrating overall consistency of results; or extrapolated evidence from studies rated as 1++ or 1+
A body of evidence including studies rated as 2+ directly applicable to the target population and demonstrating overall consistency of results; or extrapolated evidence from studies rated as 2++
Evidence level 3 or 4; or extrapolated evidence from studies rated as 2+

RCT= randomized controlled trial
The authors assessed 46 articles that each typically focused on only one of a variety of clinical aspects of performing HSCT including: timing of transplantation, pre-HSCT induction chemotherapy, donor selection and transplantation techniques including reduced-intensity conditioning versus high dose conditioning.
Three tables were presented that supplied the study design/methodology and results for each of the 46 articles. These tables are not reproduced in this NCA but can be found in the publication by Oliansky, et al, (2009). To briefly summarize: across all studies the study design/methodology ranged from single site to multi-center, from retrospective to prospective and from uncontrolled to controlled. Various combinations of therapies (pharmaceutical agents, biologicals, radiation therapy) were used for chemotherapy (for conditioning, consolidation and/or induction) and for treating praft versus host disease.
The study population was typically comprised of patients with MDS and secondary AML but could also include patients (in varying proportions) with CMML, myeloproliferative neoplasms or acute lymphocytic leukemia. The median age of the patients ranged from 24 to 62.8 years; the youngest patient was 1 year old and the oldest patient was 73 years old.
Except for the footnotes and the column indicating the references, Table 15 fully reproduces the summary of the results and recommendations from the authors.

TABLE 15: Summary of Treatment Recommendations Made by the Expert Panel for MDS (from Oliansky, et al., 2009).

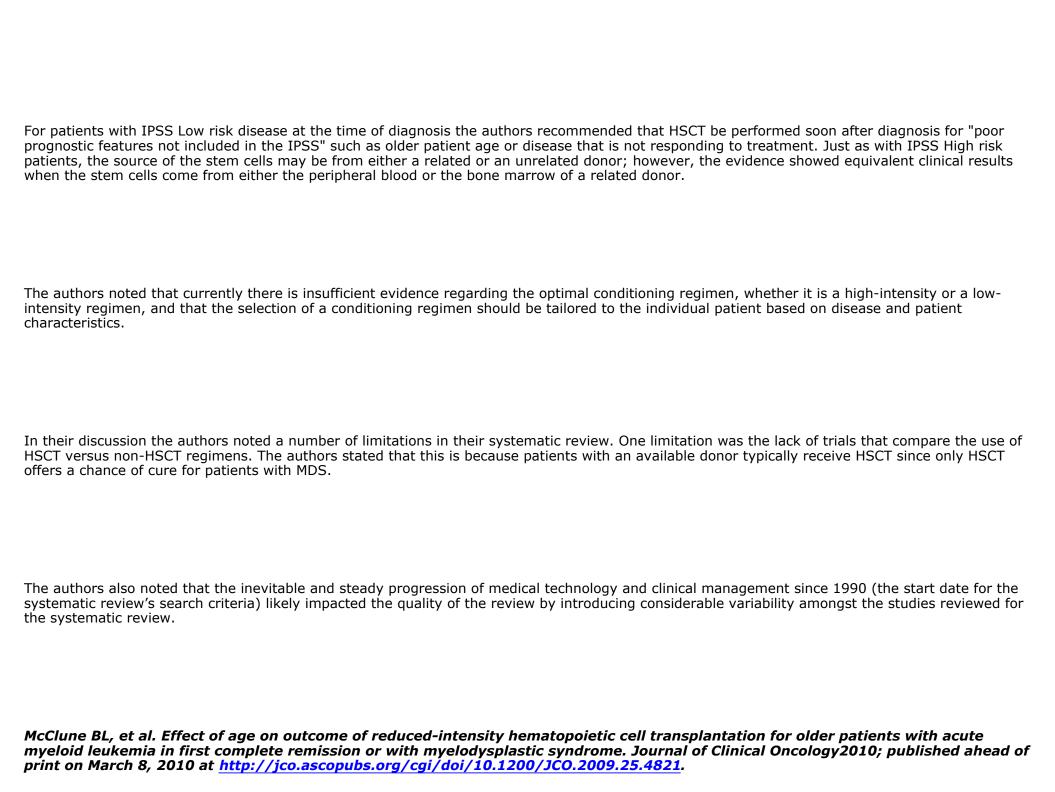
Indication for SCT	Treatment recommendation grade	Highest level of evidence	Treatment Recommendation Comments
Timing of transplantation	С	2+	Early SCT recommended for patients with IPSS score of INT-2 or high risk at diagnosis, who have a suitable donor and meet the transplant center's eligibility criteria, and for selected patients with a Low or INT-1 risk IPSS score at diagnosis who have poor prognostic features not included in the IPSS (i.e., older age, refractory cytopenias, etc.)
Pre-SCT induction chemotherapy	No recommendation	2++	In absence of RCTs there are insufficient data to make a treatment recommendation for or against pre-SCT induction chemotherapy. The decision to use pre-SCT induction therapy should be made on an individual basis.
DONOR SELECTION			
Related v. unrelated allogeneic SCT	No recommendation	2+	There is no evidence of a survival advantage based on donor relation. In clinical practice, matched related donor allogeneic SCT is recommended if available. If a matched related donor is not available, an unrelated donor allogeneic SCT may provide equivalent outcomes. The published data do not reflect the selection of donors on the basis of molecular HLA typing.
	В	2++	

Indication for SCT	Treatment recommendation grade	Highest level of evidence	Treatment Recommendation Comments
Related, unrelated, either, or unspecified allogeneic SCT			There are sufficient data demonstrating a long-term curative outcome for related and unrelated allogeneic SCT.
Autologous v. allogeneic SCT	С	2++	Based on data and expert opinion, an HLA-matched allogeneic donor (sibling, other family member, unrelated individual or cord blood) SCT is recommended if an appropriate donor is available. If an allogeneic donor is not available, and CR is achieved with induction therapy, an autologous SCT can be considered in the context of a clinical trial.
TRANSPLANTATION TECHNIQUES			
BMT v. PBSCT	В	1+	For low-risk disease, allogeneic PBSCT and BMT from related donors have equivalent outcomes. Based on one study, patients with high-risk disease may have a survival advantage with related donor allogeneic PBSCT.
Allogeneic BMT v. PBSCT	No recommendation		There is insufficient evidence to recommend bone marrow v. peripheral blood for unrelated donor allogeneic SCT.
Autologous BMT v. PBSCT	No recommendation	2+	There is no evidence of a survival advantage based on stem cell source.

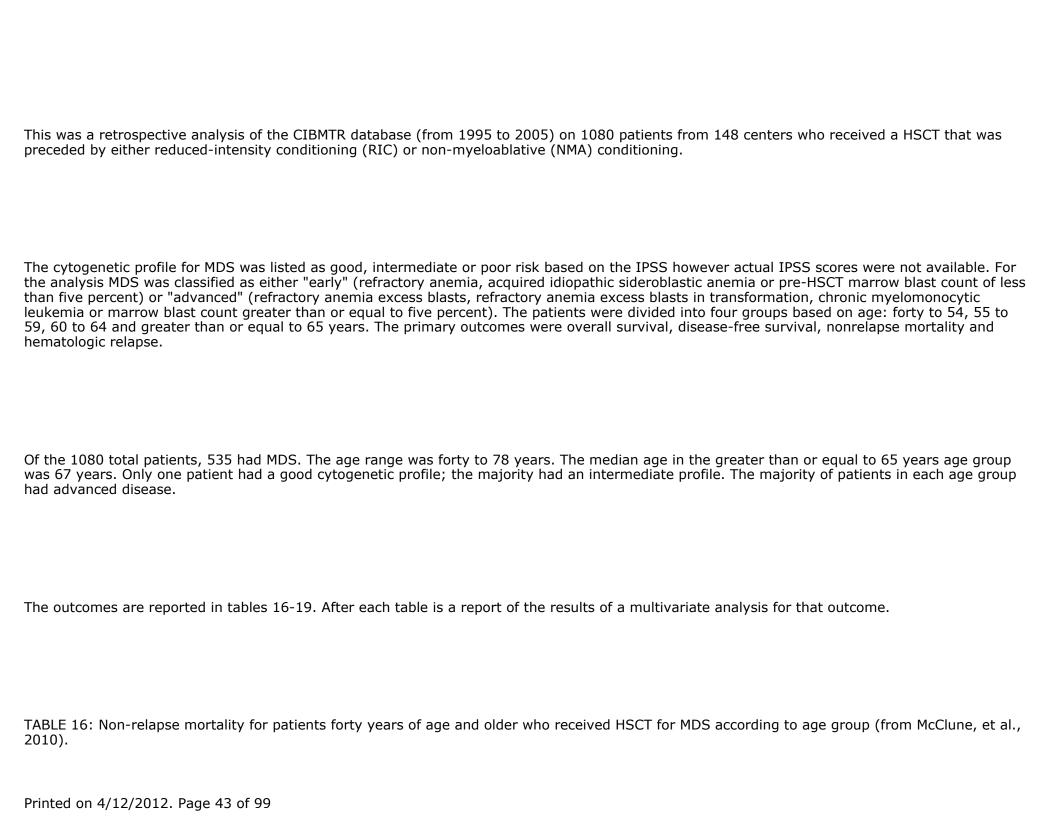
Indication for SCT	Treatment recommendation grade	Highest level of evidence	Treatment Recommendation Comments
Conditioning Regimen Comparison	No recommendation	2++	There are insufficient data to make a recommendation for optimal conditioning regimen intensity. A range of dose intensities is currently being investigated and
Reduced intensity v. high dose intensity conditioning	No recommendation	2++	the optimal approach will likely depend on disease and patient characteristics such as age and comorbidities.
Comparison of ≥ 2 high- dose regimens	No recommendation	2++	There are insufficient data to make a recommendation. There is no evidence of a survival advantage with any one high dose conditioning regimen.

SCT= stem cell transplantation; RCT= randomized controlled trial; CR= complete remission; RCT= randomized clinical trial; PBSCT= peripheral blood stem cell transplantation; BMT= bone marrow transplantation; HLA= human leukocyte antigen; IPSS= International Prognostic Scoring System; INT= intermediate

To summarize Table 15, for patients with IPSS High risk disease the authors recommended that HSCT be performed soon after diagnosis if a suitable donor is available and the patient meets the eligibility criteria of a transplant center. The source of the stem cells may be from either a related or an unrelated donor since the evidence showed that a "long-term curative outcome" after allogeneic HSCT is associated with either source. The evidence also suggested that there may be a greater chance of patient survival when the stem cells come from the peripheral blood of a related donor. The recommendations are based on B and C strength evidence, which results from an overall body of evidence that the authors rated as having a quality of 2+ to 2++.



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	40-54 years	55-59 years	60-64 years	65 years and older
% Non-relapse mortality (95% CI)				
100-days	17 (12-22)	17 (12-24)	13 (8-20)	19 (10-30)
1-year	29 (23-36)	32 (25-40)	32 (24-40)	35 (22-48)
2-year	33 (27-40)	39 (31-47)	35 (27-44)	39 (26-53)

Multivariate analysis was performed for both MDS and AML combined. The one-year non-relapse mortality was adversely affected by a lower Karnofsky Performance Score (i.e., a more debilitated patient), a diagnosis of MDS (regardless of cytogenetic profile) and a worsening HLA disparity (statistical significance not provide). Patient age did not impact non-relapse mortality. Use of a non-myeloablative conditioning regimen was associated with a borderline lower risk of non-relapse mortality (OR, 0.75, 95% CI, 0.57 - 1.0; p = 0.05). The most common reason for death for both MDS and AML patients was relapse (33%) followed by infection (21%).

TABLE 17: Relapse at 2 years for patients forty years of age and older who received HSCT for MDS according to age group (from McClune, et al., 2010).

	40-54 years	55-59 years	60-64 years	65 years and older
%Relapse at 2 years (95% CI)				
	28 (22-34)	29 (22-37)	29 (21-38)	25 (14-38)

No statistically significant differences seen.

Multivariate analysis was performed for both MDS and AML combined. The relapse at two years was statistically significantly higher for patients who received non-myeloablative conditioning rather than reduced-intensity conditioning (OR, 1.46, 95% CI, 1.15 - 1.85; p = 0.002) and for patients with an unfavorable/poor-risk cytogenetic profile (OR, 1.57, 95% CI, 1.04 - 2.35; p < 0.03). Patients with early MDS had a lower two-year relapse than patients with advanced MDS (OR, 0.43, 95% CI, 0.26 - 0.714; p < 0.001). Patient age did not impact relapse.

TABLE 18: Disease-free survival for patients forty years of age and older who received HSCT for MDS according to age group (from McClune, et al., 2010).

	40-54 years	55-59 years	60-64 years	65 years and older
%Disease-free survival (95% CI)				
1-year	44 (37-51)	40 (32-49)	43 (34-52)	42 (29-56)
2-year	39 (32-46)	32 (24-40)	35 (27-45)	36 (23-49)

No statistically significant differences seen.

Multivariate analysis was performed for both MDS and AML combined. Disease-free survival was adversely affected for patients with an unfavorable/poor-risk cytogenetic profile (OR, 1.27, 95% CI, 1.01 - 1.61; p = 0.05) and greater HLA disparity (p = 0.05 across the group). Patient age did not impact disease-free survival.

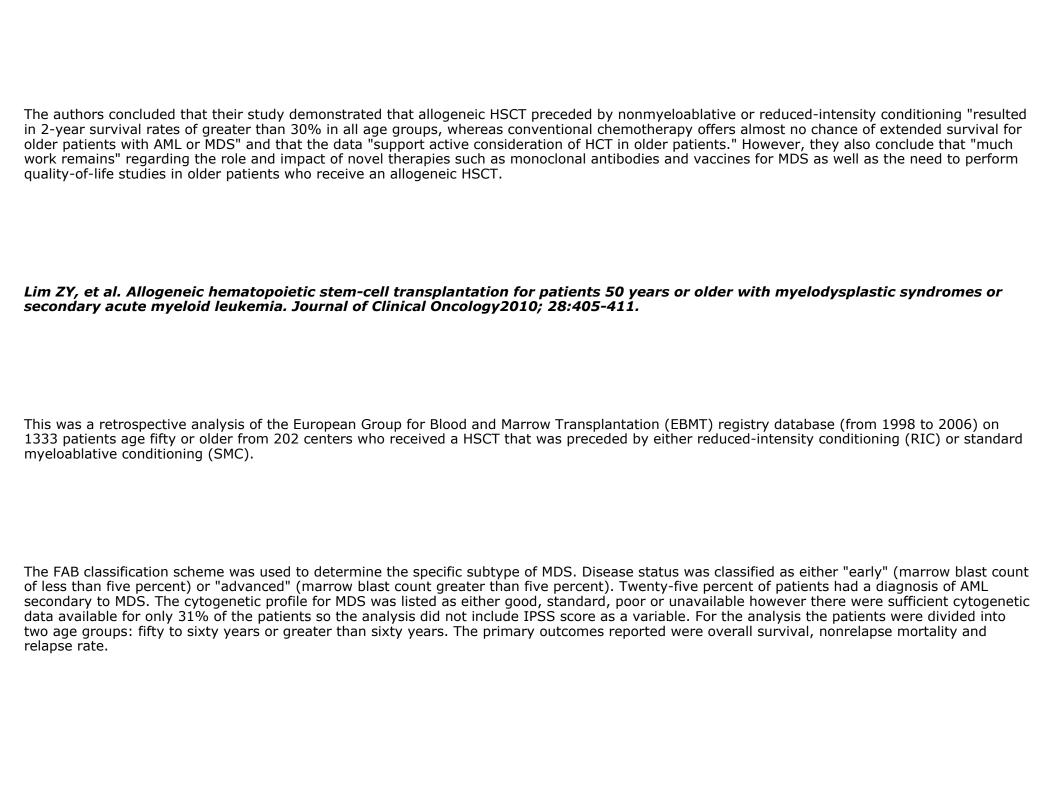
TABLE 19: Overall survival at 2 years for patients forty years of age and older who received HSCT for MDS according to age group (from McClune, et al., 2010).

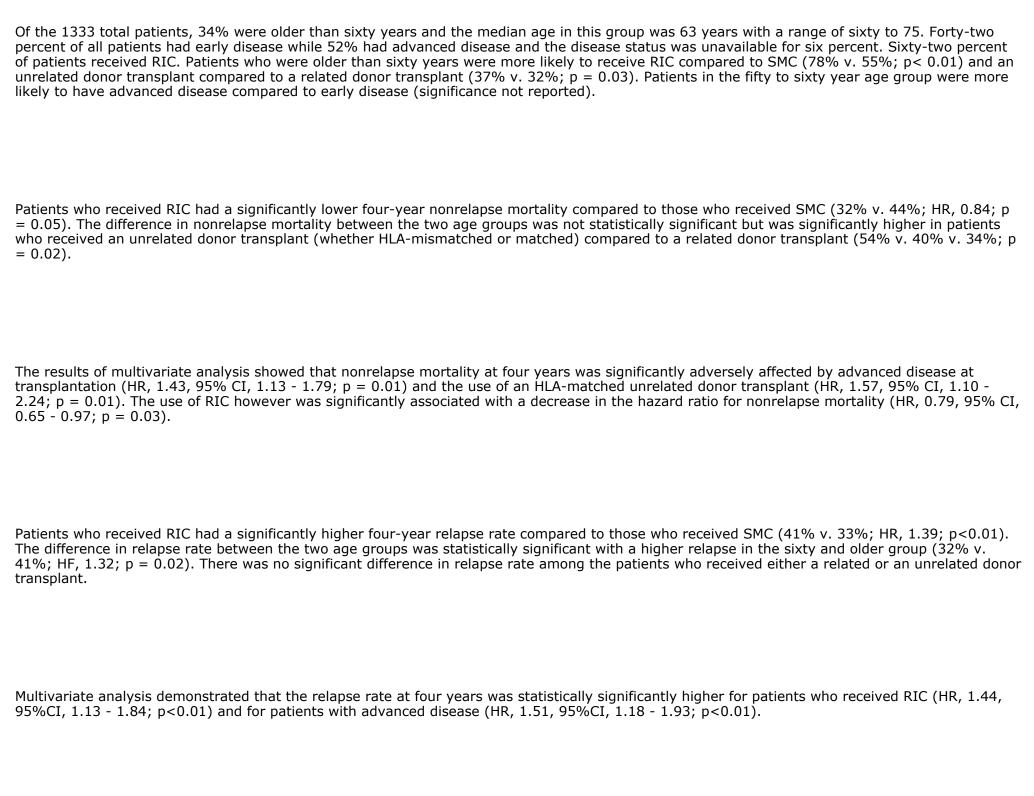
	40-54 years	55-59 years	60-64 years	65 years and older
%Overall survival at 2 years (95% CI)				
	42 (35-49)	35 (27-43)	45 (36-54)	38 (25-51)

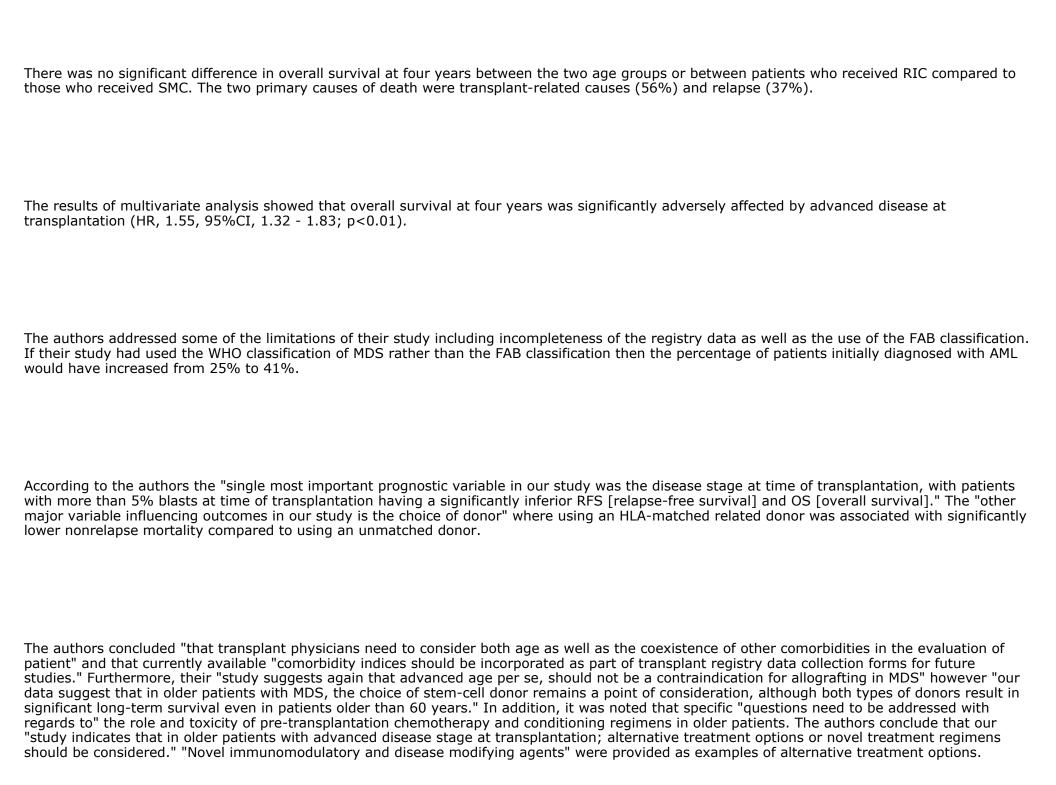
No statistically significant differences seen.

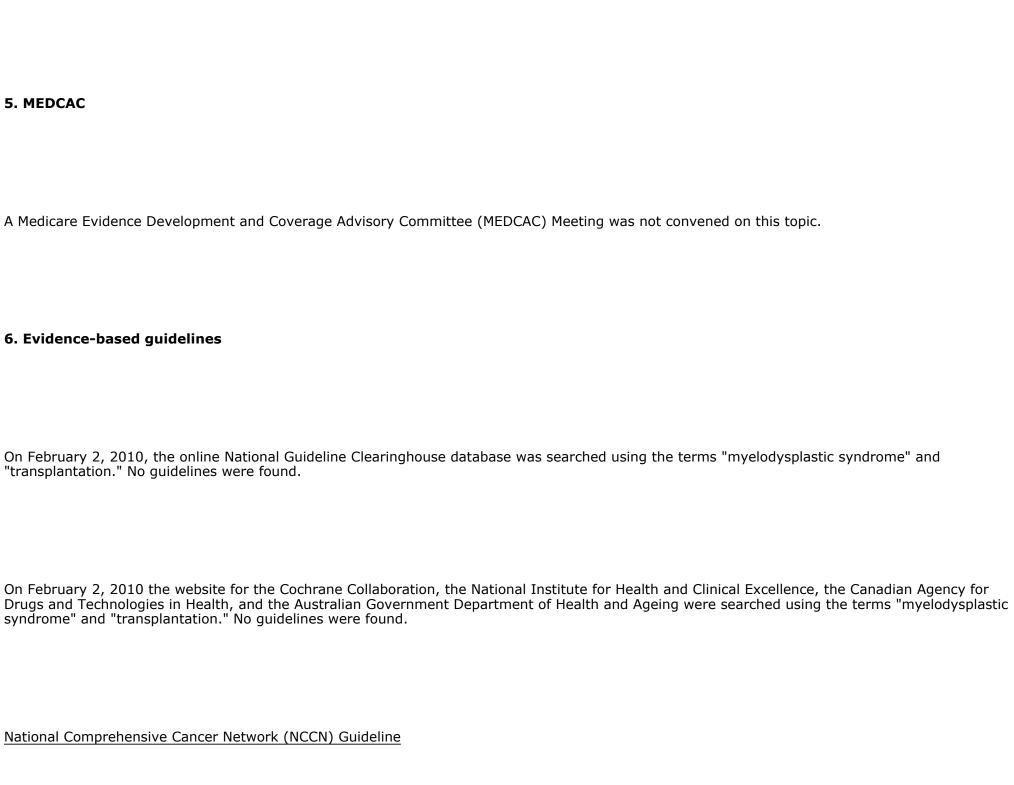
Multivariate analysis was performed for both MDS and AML combined. Overall survival at two-years was adversely affected for patients with a lower Karnofsky Performance Score (i.e., a more debilitated patient; OR, 1.63, 95% CI, 1.21 - 2.20; p = 0.001) and for patients with an unfavorable/poorrisk cytogenetic profile (OR, 2.01, 95% CI, 1.39 - 2.91; p < 0.001). Patient age did not impact overall survival at two-years.

The authors noted that "transplantation toxicity, relapse, and survival for older adults are not significantly different than those for younger adults undergoing a similar NMA or RIC allogeneic HCT" while acknowledging "that small patient numbers may confound recognition of small differences in outcomes; however, these encouraging data help confirm the overall safety and tolerability of the procedure, even in the oldest group." The authors also noted the uncertainty that remains regarding the best conditioning regimen for allogeneic HSCT and stated that "carefully designed prospective trials are essential to determine the contribution of a specific conditioning regimen to success disease control."





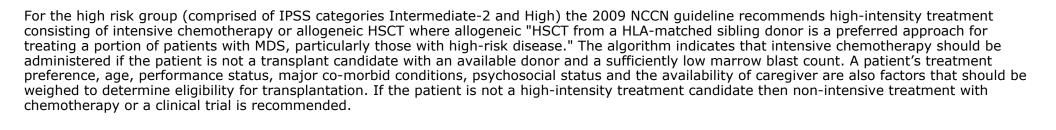




CMS is aware that the NCCN publishes a clinical practice guideline titled Myelodysplastic Syndromes. (NCCN Guideline, 2009) The most recent version was released on August 26, 2009. The guideline is prepared by the NCCN Myelodysplastic Panel, which is comprised of experts in medical oncology, hematology/hematology oncology, internal medicine and/or pathology from various centers throughout the United States. The NCCN uses a "Categories of Evidence and Consensus" to classify its recommendations. There are 4 categories (1, 2A, 2B and 3) with Category 1 providing the strongest strength of recommendation. All recommendations are classified as Category 2A in the Myelodysplastic Syndromes guideline unless otherwise noted. Category 2A means that the "recommendation is based on lower-level evidence and there is uniform NCCN consensus."

The 2009 NCCN guideline notes the historical use of the FAB classification and then presents the current use of the 2008 WHO classification of MDS. This classification also includes myeloproliferative neoplasms. The guideline continues by presenting the IPSS classification system. In the Background section titled "Classification of MDS" of this NCA, Table 4 (which is a table from the 2009 NCCN guideline) presents two types of outcome data on untreated patients in each IPSS risk group: median survival in years and the number of years it would take for 25% of the MDS patients to progress to AML. These outcomes range from 5.7 and 9.4 years, respectively, for the low risk untreated patients, to 0.4 and 0.2 years, respectively, for the high risk group. The 2009 NCCN guideline remarks that both "for survival and AML evolution, the IPSS showed statistically greater prognostic discriminating power than earlier classification methods, including the FAB system." Of note, in its discussion section the 2009 NCCN guideline comments that astudy by Alessandrino, et al. (2008) "retrospectively evaluated the impact of WHO classification and WPSS on the outcome of patients who underwent allogeneic HSCT. Data suggest that lower risk patients (based on WPSS risk score) do well with allogeneic HSCT with a 5-year overall survival of 80% whereas those with 5-20% marrow blast have only 25-28% 5 year overall survival." The 2009 NCCN guideline, however, uses the IPSS classification to plan treatment options.

The 2009 NCCN guideline stratifies its treatment algorithms by risk group with the low risk group (comprised of the IPSS categories Low and Intermediate-1) presented separately from the high risk group (comprised of IPSS categories Intermediate-2 and High). For the Low and Intermediate-1 categories the 2009 NCCN guideline recommends that HSCT should generally be considered after numerous other types of generally low-intensity treatments have been administered unsuccessfully such as supportive care with transfusions, antibiotics, iron chelation and growth stimulating hormones (e.g., erythropoietin) and various types of chemotherapy including hypo-methylating agents, biologic response modifiers and immunosuppressive agents. Participation in a clinical trial was the other recommendation for patients in this low risk group who have disease that is unresponsive to low-intensity treatment.

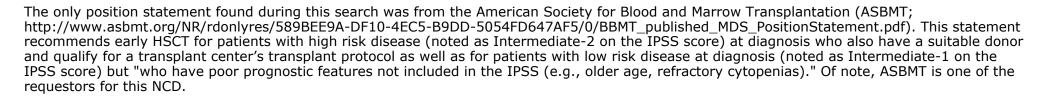


The 2009 NCCN guideline discusses the issue of myeloablative conditioning versus the use of reduced intensity conditioning (RIC) by noting that myeloablative conditioning regimens can be used for younger patients while non-myeloablative conditioning or RIC "is preferable in older individuals." Based on the results from clinical studies the guideline states that a patient's "age and disease status generally dictate the type of conditioning to be utilized," where "disease status" consists of the blast count. Additionally, variations should "be considered by the individual transplant physician based on these features and the specific regimen utilized at that center."

Finally, the guideline concludes with the following recommendation for additional research: "Progress toward improving management of MDS has occurred over the past few years and more such advances are anticipated using these guidelines as a framework for coordination of comparative clinical trials."

## 7. Professional Society Position Statement

The websites for each of the following organizations was searched for a position statement: the National Marrow Donor Program, the American Society for Blood and Marrow Transplantation, the American Cancer Society, the American Cancer Society Cancer Action Network, the AABB, the American Society of Hematology, the American Society of Clinical Oncology, the Aplastic Anemia and MDS International Foundation, the Blood and Marrow Transplant Information Network, the National Bone Marrow Transplant Link, the Bone Marrow Foundation, and the Leukemia and Lymphoma Society.



## 8. Public Comments

CMS uses the initial public comments to inform its proposed decision. Public comments that give information on unpublished evidence such as the results of individual practitioners or patients are less rigorous and therefore less useful for making a coverage determination. Public comments that contain personal health information will not be made available to the public. CMS responds in detail to the public comments on a proposed decision when issuing the final decision memorandum.

## A. Initial 30-day comment period

CMS received 264 comments during the initial 30-day public comment period. Comments that were submitted via the CMS coverage website, with the exception of one comment which contained personal health information, may be viewed using the following link: <a href="http://www.cms.gov/mcd/viewpublic comments.asp?ncd\_ID=238">http://www.cms.gov/mcd/viewpublic comments.asp?ncd\_ID=238</a>. The summary of those comments can be found in our proposed decision memorandum which is published on the CMS website at <a href="http://www.cms.gov/mcd/viewdraftdecisionmemo.asp?id=238">http://www.cms.gov/mcd/viewdraftdecisionmemo.asp?id=238</a>.

B. Public Comment Period on the Proposed Decision
CMS received a total of 14 public comments on the proposed decision. Commenters included a member of Congress, six from the general public (relatives/friends of patients), three from providers and four from healthcare-related professional organizations/societies. We did not receive any published evidence that had not already been reviewed in the proposed decision.
The comments varied widely, with the preponderanceexpressing satisfaction with the use of CED, citing the decision as a step in the right direction. Many would have preferred national coverage without a study requirement, however. There were a few comments asserting outright support of the decision based on lack of evidence in use of HSCT for patients with MDS. The majority of comments against the proposed decision were from individuals in the general public. Many of these commenters focused on the proposed noncoverage under §1862(a)(1)(A); in their comments there was no reference to, or acknowledgement of, our proposal to use CED and cover HSCT for MDS in a clinical study.
Comments which support the proposed decision:
We received favorable comments from a member of Congress and America's Health Insurance Plans (AHIP) who strongly supported our proposed decision. One commenter states that there are few clinical treatments proven effective in this area but urges CMS to be prompt and realistic in review of the clinical study design. AHIP agrees with CMS that "there is a lack of evidence on the efficacy of this treatment for myelodysplastic syndrome for patients 65 and older". They also acknowledge that there remain questions related to appropriate populations and treatment approaches.

desponse:
We thank the commenters for their support. We agree that, based on a lack of sound evidence, there is need for greater clinical study in this area. We also support imposition of reasonable study criteria which can be promptly implemented. We have committed to working cooperatively with the xternal requestors to assist with efforts to implement a feasible study design.
Comments which are opposed to the proposed decision or parts of the proposed decision:
Comment:
one commenter wrote that there should be no national coverage policy and that local physicians should determine treatment on a case-by-case bas
Pesponse:

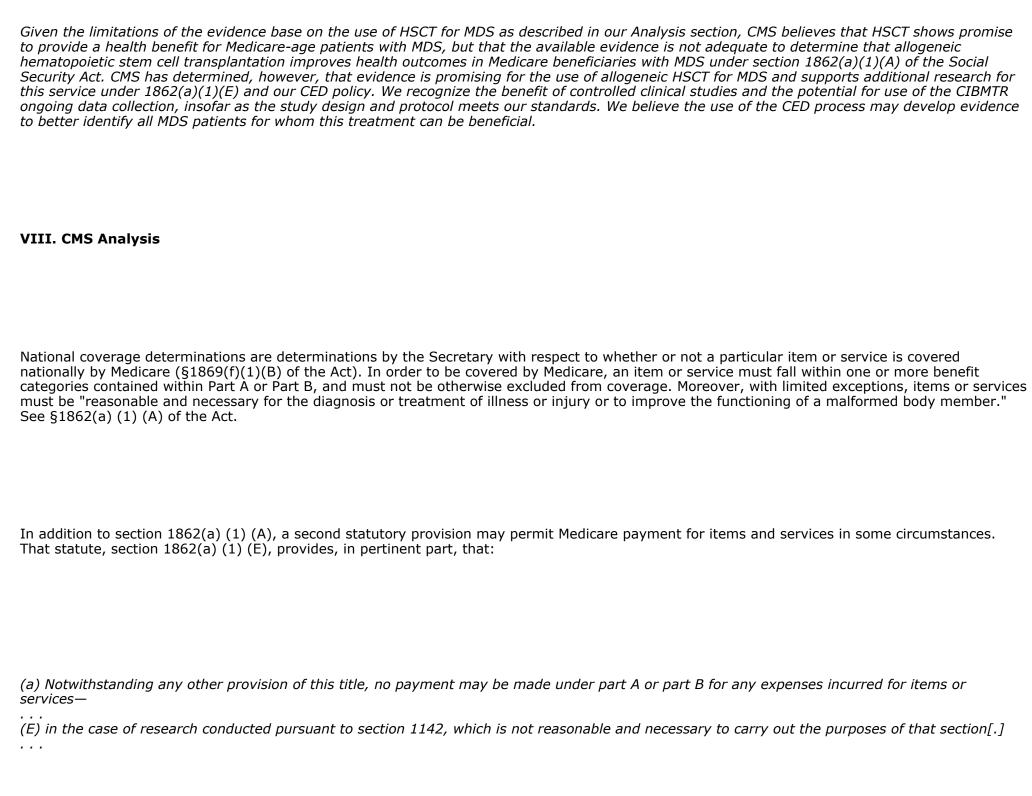
We disagree. CMS opened this NCD reconsideration pursuant to a request for nationally consistent Medicare coverage policy, and we are acting within the Secretary's authority to make NCDs.
Comment:
One commenter remarked on Agent Orange exposure in Vietnam and stated that the VA (Veterans Administration) views MDS as a difficult form of
nemia.
Response:
This comment is outside of the scope of this decision and we will not address it here.
Comment:

One commenter, a provider, claims the proposed decision adversely affects patients in a rural area, contending that it precludes any local coverage for those who need HSCT. The commenter alleges that the majority of patients do not have access to clinical trials due to travel logistics and geographic location.
Response:
The appropriate clinical study methodology (or methodologies) is dependent on the evidentiary questions to be answered. Thus, the CED requirement may, if scientifically appropriate, be fulfilled in certain cases by prospective clinical studies that are more generally accessible than facility-based randomized clinical trials (RCTs) As we note in the decision memorandum, CMS does not require that all beneficiaries be enrolled in a RCT to fulfill the requirements of CED. CMS is committed to working with stakeholders to enable broad access to clinical studies that would satisfy the CED requirement. The commenter is correct that local coverage is not permitted to conflict with NCDs.
Comment:
One commenter claimed that we have characterized MDS as a "benign anemia."
Response:

We disagree. Nowhere in the proposed decision memorandum have we characterized MDS as a benign anemia.
Comment:
Several comments from patients and their friends/relatives expressed disappointment with the proposed decision to require conditions of national coverage instead of unfettered national coverage, one referring to it as obsolete. Most of the comments did not address our proposal to use CED, while one asserted CED does not go far enough. Some questioned the standing national coverage for acute myeloid leukemia (AML), a disease for which MDS is typically the precursor, saying that AML is less responsive to HSCT.
Response:
The prior coverage determination for HSCT treatment of AML is outside the scope of our current decision. Commenters did not suggest that Medicare coverage of HSCT for AML should be curtailed, and we will not address it further here.
While we appreciate the desire by some commenters for unrestricted national coverage and agree HSCT has the potential to benefit some elderly patients, our extensive review of the available evidence did not support full coverage under 1862(a)(1)(A) of the Act. The use of CED expands the potential universe of beneficiaries eligible for coverage. We have, based on evidence, in this instance actually provided broader coverage than was requested. The requestors had asked for national coverage not for all MDS patients, but for those in high risk groups or with high risk factors. We believe the use of the CED process will develop evidence to better identify all MDS patients for whom this treatment will be beneficial.

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Comment:
Several commenters, some of whom were requestors of this NCD, express disappointment with lack of unrestricted national coverage. They largely issert that there is evidence to support unrestricted coverage for allogeneic HSCT for MDS. However, they express satisfaction with our proposed lecision for coverage with evidence development. These commenters include the National Marrow Donor Program and the American Society of Blood and Marrow Transplantation (NMDP/ASBMT), the Alliance of Dedicated Cancer Centers (the "Cancer Centers"), the Leukemia and Lymphoma Society and the University of Miami Cancer Center. Also, they generally acknowledge the need to demonstrate through clinical evidence the curative potential rom this therapy. The NMDP/ASBMT remarked on the ongoing data collection and submission mandates through the CIBMTR as established under he Stem Cell Therapeutic and Research Act of 2005 and suggest using the CIBMTR study to meet our NCD and CED requirements. The Cancer Centers referred to our proposed decision and asked us to reconsider the evidence and allow for unrestricted national coverage, i.e., without nandated clinical studies. They asked whether we believe there would be a subset of the MDS patients for which HSCT would be appropriate, e.g., sigh risk patients.
Response:
While we appreciate the desire for unrestricted national coverage and agree HSCT has the potential to benefit some elderly patients, our extensive review of the available evidence did not support full coverage. Though these commenters expressed disappointment with the proposed decision, we relieve that these comments support, in the absence of unrestricted coverage, the use of CED as an appropriate approach to evaluate HSCT for MDS. Commenters acknowledged that there is some evidence of benefit but further clinical study is needed. In fact the requestors asked for national coverage not for all MDS patients, but for those in high risk groups or with high risk factors.



Section 1142 describes the authority of the AHRQ.
Under the authority of § 1862(a)(1)(E), Medicare may cover under coverage with evidence development/coverage with study participation (CED) certain items or services for which the evidence is not adequate to support coverage under §1862(a)(1)(A), and where additional data gathered in the context of clinical care would further clarify the impact of these items and services on the health of Medicare beneficiaries. CMS has described CED/ in greater detail in guidance document available at <a href="http://www.cms.gov/mcd/ncpc_view_document.asp?id=8">http://www.cms.gov/mcd/ncpc_view_document.asp?id=8</a> . CED allows CMS to provide coverage based on a determination that an item or service is only reasonable and necessary when it is provided within a research setting where there are added safety, patient protections, monitoring, and clinical expertise.
Under section 1142, research may be conducted on the outcomes, effectiveness, and appropriateness of health care services and procedures to identify the manner in which diseases, disorders, and other health conditions can be prevented, diagnosed, treated, and managed clinically.
As a general matter, CED is to be used in rare instances. For some items or services, CMS may determine that the evidence is preliminary and no reasonable and necessary for Medicare coverage under section 1862(a)(1)(A), but, if the following criteria are met CED/ might be appropriate:
<ul> <li>The evidence includes assurance of basic safety;</li> <li>The item or service has a high potential to provide significant benefit to Medicare beneficiaries; and</li> <li>There are significant barriers to conducting clinical trials.</li> </ul>
These research studies will be rigorously designed and include additional protections and safety measures for beneficiaries.

Regarding these 3 criteria:

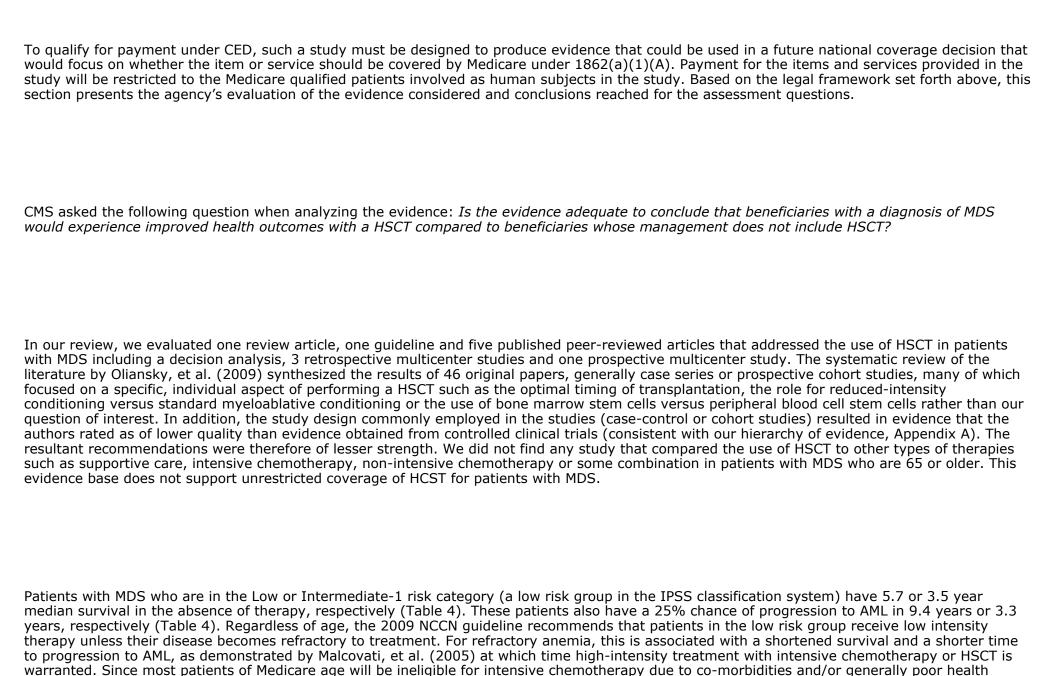
1.

The varying prognosis for MDS needs to be weighed against the significant chance for morbidity and mortality after HSCT. In the studies evaluated, the health outcomes examined (treatment-related mortality, non-relapse mortality, progression-free survival, relapse rate and overall survival) attest to the significant morbidity and mortality associated with HSCT. Martino, et al. (2006) showed a nonrelapse mortality rate of 22% and a relapse rate of 45% three years after HSCT for patients who received reduced-intensity conditioning. Lim, et al. (2010)showed a four-year nonrelapse mortality rate of 32% and a relapse rate of 41% three years after HSCT for patients who received reduced-intensity conditioning. Although the individual rates of these two health outcomes may differ between studies, a reduction in nonrelapse mortality and an increase in relapse rate in patients given reduced-intensity conditioning appear to be a consistent finding in the literature as noted in McClune, et al. (2010) and Lim, et al. (2010). Results from these two studies also demonstrated that this relationship occurs in patients 65 years and as older as well as in younger patients. However, the evidence also points to a decreased health benefit from HSCT with increasing patient age and with worsening disease.

While allogeneic stem cell transplantation has been performed for years and has known risks (including death), the risks may be evaluated by the patient and accepted in the context of a clinical study that include additional protections and safety measures for beneficiaries.

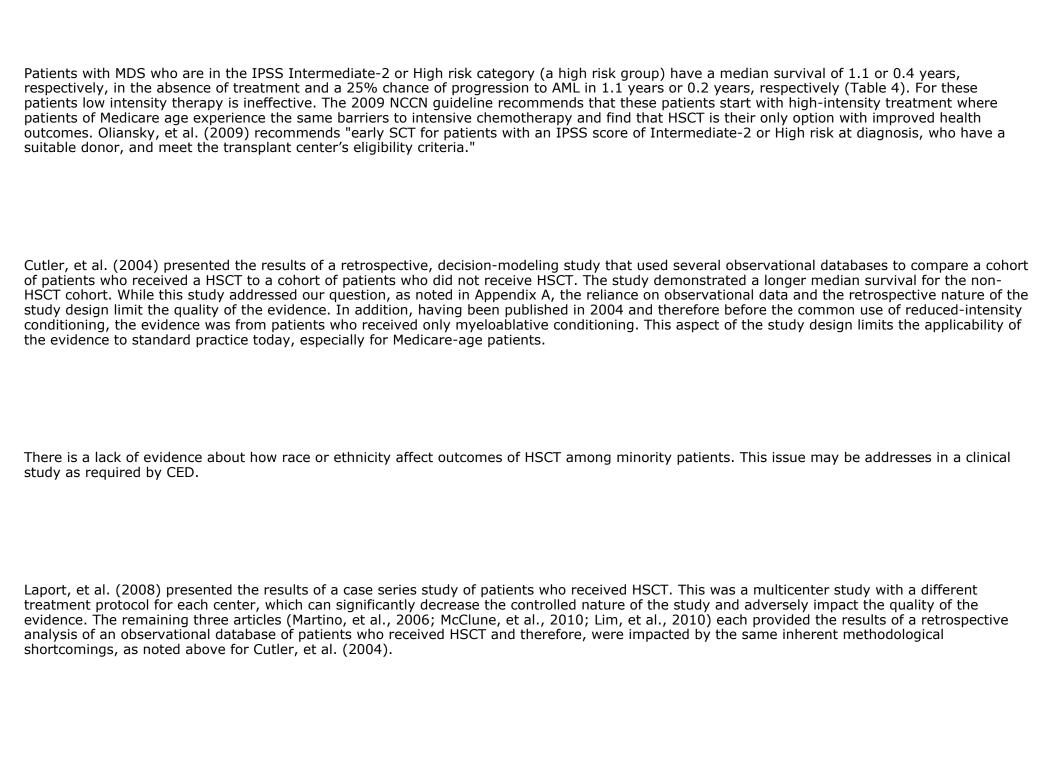
- 2. Several authors, as well as professional societies quoted in this decision memorandum have cited the potential for allogeneic stem cell transplantation to be "curative" for MDS, albeit in a limited proportion of patients. Given the poor prognosis for older patients with MDSwho are in the IPSS High risk category as well as the lack of treatment alternatives other than supportive care, CMS believes that HSCT has the potential to provide a health benefit. For olderpatients with MDS who are in the IPSS Low risk category, but who have disease that has become refractory to standard treatment, and who have a poor prognosis and lack treatment alternatives other than supportive care, CMS believes that HSCT has the potential to provide a health benefit.
- 3.

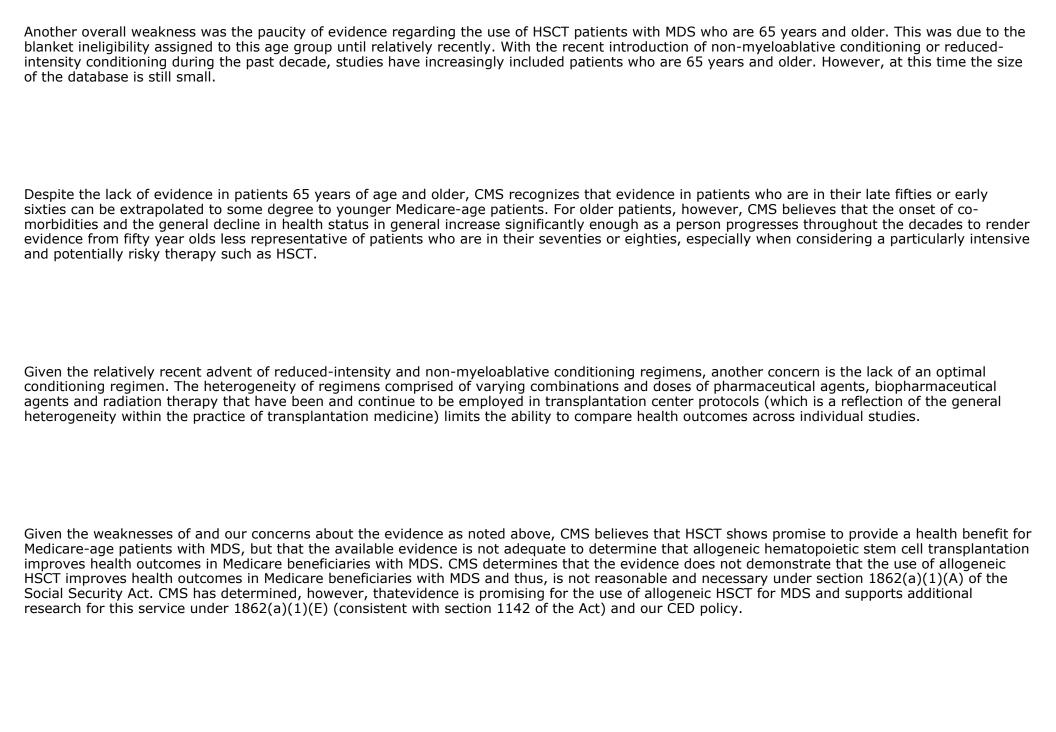
Despite the repeated call in the clinical literature for further research, as noted in numerous published articles including Oliansky, et al. (2009), Laport, et al. (2008) and McClune, et al. (2010) the evidence review is notable for an absence of comparative trials of treatment for MDS. Two commonly statedsignificant barriers to conducting comparative LP clinical trials are the poor prognosis for patients with High risk MDS prior to HSCT and the commonly-held belief in the transplant community (as noted by several authors and professional societies quoted in this memorandum) that HSCT is the only "cure" for MDS.

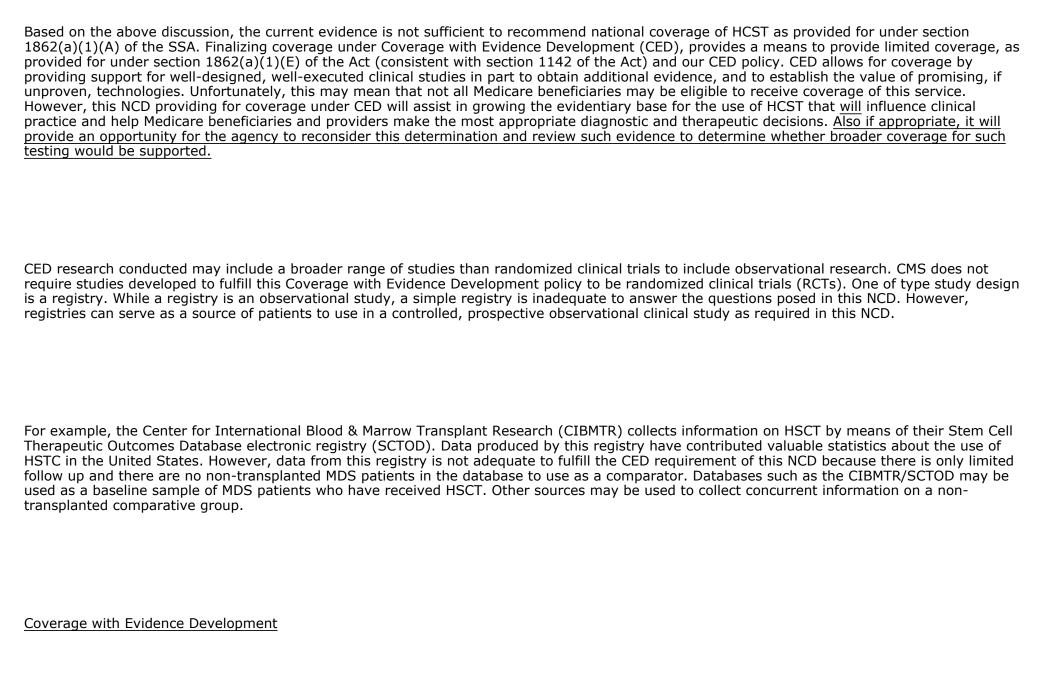


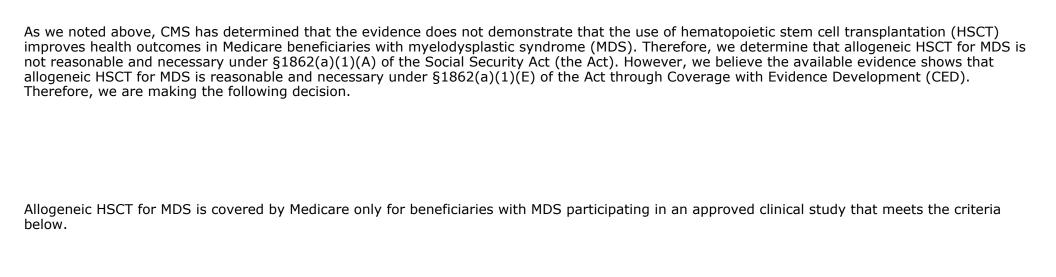
status, HSCT may be their only potential option. Oliansky, et al. (2009) recommend HSCT "for selected patients with a Low or Intermediate-1 risk

IPSS score at diagnosis who have poor prognostic features not included in the IPSS (i.e., older age, refractory cytopenias, etc.)."









A clinical study seeking Medicare payment for allogeneic hematopoietic stem cell transplantation for myelodysplastic syndrome pursuant to Coverage with Evidence Development (CED) must address one or more aspects of the following questions.

Prospectively, compared to Medicare beneficiaries with MDS who do not receive hematopoietic stem cell transplantation, do Medicare beneficiaries with MDS who receive hematopoietic stem cell transplantation have improved outcomes as indicated by:

- · relapse free mortality,
- progression free survival,
- relapse, and
- overall survival?

Prospectively, in Medicare beneficiaries with MDS who receive hematopoietic stem cell transplantation, how do International Prognostic Scoring System (IPSS) score, patient age, cytopenias and comorbidities predict the following outcomes:

- · relapse free mortality,
- progression free survival,
- relapse, and
- overall survival?

Prospectively, in Medicare beneficiaries with MDS who receive hematopoietic stem cell transplantation, what treatment facility characteristics predict meaningful clinical improvement in the following outcomes:

- relapse free mortality,
- · progression free survival,
- relapse, and
- overall survival?

CED-Coverage with Study Participation (CSP) research conducted may include a broader range of studies than randomized clinical trials to include observational research. CMS does not require studies developed to fulfill this Coverage with Evidence Development policy to be randomized clinical trials (RCTs). Many papers address methods of compensating for selection bias in observational studies. Prospective nonrandomized studies require careful design and expertise to develop statistical methods that will minimize the effects of differential selection. Studies that qualify for CED should contain a section in the protocol that describes the statistical methods used to address this problem.

The clinical study must adhere to the following standards of scientific integrity and relevance to the Medicare population:

- a. The principal purpose of the research study is to test whether a particular intervention potentially improves the participants' health outcomes.
- b. The research study is well supported by available scientific and medical information or it is intended to clarify or establish the health outcomes of interventions already in common clinical use.
- c. The research study does not unjustifiably duplicate existing studies.
- d. The research study design is appropriate to answer the research question being asked in the study.
- e. The research study is sponsored by an organization or individual capable of executing the proposed study successfully.
- f. The research study is in compliance with all applicable Federal regulations concerning the protection of human subjects found at 45 CFR Part 46. If a study is regulated by the Food and Drug Administration (FDA), it must be in compliance with 21 CFR parts 50 and 56.
- g. All aspects of the research study are conducted according to appropriate standards of scientific integrity (see http://www.icmje.org).
- h. The research study has a written protocol that clearly addresses, or incorporates by reference, the standards listed here as Medicare requirements for CED coverage.
- i. The clinical research study is not designed to exclusively test toxicity or disease pathophysiology in healthy individuals. Trials of all medical technologies measuring therapeutic outcomes as one of the objectives meet this standard only if the disease or condition being studied is life threatening as defined in 21 CFR § 312.81(a) and the patient has no other viable treatment options.
- j. The clinical research study is registered on the Clinical Trials.gov website by the principal sponsor/investigator prior to the enrollment of the first study subject.

- k. The research study protocol specifies the method and timing of public release of all pre-specified outcomes to be measured including release of outcomes if outcomes are negative or study is terminated early. The results must be made public within 24 months of the end of data collection. If a report is planned to be published in a peer reviewed journal, then that initial release may be an abstract that meets the requirements of the International Committee of Medical Journal Editors
  - (http://www.icmje.org). However a full report of the outcomes must be made public no later than three (3) years after the end of data collection.
- I. The research study protocol must explicitly discuss subpopulations affected by the treatment under investigation, particularly traditionally underrepresented groups in clinical studies, how the inclusion and exclusion criteria effect enrollment of these populations, and a plan for the retention and reporting of said populations on the trial. If the inclusion and exclusion criteria are expected to have a negative effect on the recruitment or retention of underrepresented populations, the protocol must discuss why these criteria are necessary.
- m. The research study protocol explicitly discusses how the results are or are not expected to be generalizable to the Medicare population to infer whether Medicare patients may benefit from the intervention. Separate discussions in the protocol may be necessary for populations eligible for Medicare due to age, disability or Medicaid eligibility.

Consistent with section 1142 of the Social Security Act, AHRQ supports clinical research studies that CMS determines meet the above-listed standards and address the above-listed research questions.

CMS acknowledges the role of the accreditation organizations in facilitating the development of and maintaining the presence of high quality policies, procedures and practices in the field of transplantation. Both the NMDP and the FACT-JACIE have established provider and facility standards as noted previously in the Introduction to section VII.

The facility (i.e., transplant center) participation criteria are set forth by the NMDP. These include requirements for the facility as well as the personnel and transplant team, including physician qualifications and board certification requirements. There are specific standards related to support services, policies and procedures, patient advocacy and administrative compliance rules. The NMDP also established a volume requirement mandate that requires that the applicant center has performed ten allogeneic transplants for at least ten different patients in 24 months or for twenty different patients within the last twelve months. The NMDP standards are specific to unrelated allogeneic transplantation and apply to all donor recruitment, donor screening, and collection storage processing release and transplantation and administration of hematopoietic stem cells facilitated through the NMDP.

The key clinical program standards are set forth by the FACT-JACIE, two organizations that maintain separate and parallel accreditation processes, but have jointly established international standards related to the primary functions within a transplant program: the clinical program, collection facility and processing facility. The FACT-JACIE standards provide minimal guidelines for programs facilities and individuals. These include clinical program, personnel quality management, policies and procedures, clinical research and data management. The clinical program accreditation requires that there be ten new allogeneic HSCT patients per year and the requirement must be met during the two month period immediately preceding the application.

In addition, a federally mandated outcomes data collection for HSCT for MDS captures data on all U.S. recipients, including Medicare beneficiaries and was enacted in accordance with the Stem Cell Therapeutic and Research Act of 2005 (U.S. Public Law 109-129). The CIBTMR was awarded a contract by HRSA (Health Resources and Services Administration) to administer the Stem Cell Outcomes Database (SCTOD). For all U.S. allograft recipients, a standard dataset must be submitted to the CIBTMR. The SCTOD collects data on the allogeneic transplants in order to increase safety, efficacy and availability of HSCT. All participating centers provide a dataset of their recipients' pre-and post- transplant at 100-day, 6-month, and annual interviews. The data set known as the transplant essential data (TED) encompasses in part, both the dataset required for submission to SCTOD as well as for the FACT-JACIE accreditations. Through the CIBTMR a worldwide network of HSCT centers currently share data on HSCT outcomes and maintains a clinical database with information for more than 280,000 recipients.

The role of the statutorily-mandated data collection program administered by CIBMTR is and will continue to be critically important. The collection and analysis of data on patients with MDS who are of Medicare age and who receive a HSCT will permit the reassessment and revision of this coverage policy.

## **IX.** Conclusion

CMS has determined that the evidence does not demonstrate that the use of allogeneic hematopoietic stem cell transplantation (HSCT) improves health outcomes in Medicare beneficiaries with myelodysplastic syndrome (MDS). Therefore, we determine that allogeneic HSCT for MDS is not reasonable and necessary under  $\S1862(a)(1)(A)$  of the Social Security Act (the Act). However, we believe the available evidence shows that allogeneic HSCT for MDS is reasonable and necessary under  $\S1862(a)(1)(E)$  of the Act through Coverage with Evidence Development (CED). Therefore, we are making the following decision.

Allogeneic HSCT for MDS is covered b	y Medicare only for beneficiario	es with MDS participating in an	approved clinical study that	meets the criteria
below.				

A clinical study seeking Medicare payment for allogeneic hematopoietic stem cell transplantation for myelodysplastic syndrome pursuant to Coverage with Evidence Development (CED) must address one or more aspects of the following questions.

- 1. Prospectively, compared to Medicare beneficiaries with MDS who do not receive hematopoietic stem cell transplantation, do Medicare beneficiaries with MDS who receive hematopoietic stem cell transplantation have improved outcomes as indicated by:
  - o relapse free mortality,
  - progression free survival,
  - o relapse, and
  - o overall survival?

2.

Prospectively, in Medicare beneficiaries with MDS who receive hematopoietic stem cell transplantation, how do International Prognostic Scoring System (IPSS) score, patient age, cytopenias and comorbidities predict the following outcomes:

- o relapse free mortality,
- o progression free survival,
- o relapse, and
- o overall survival?

3.

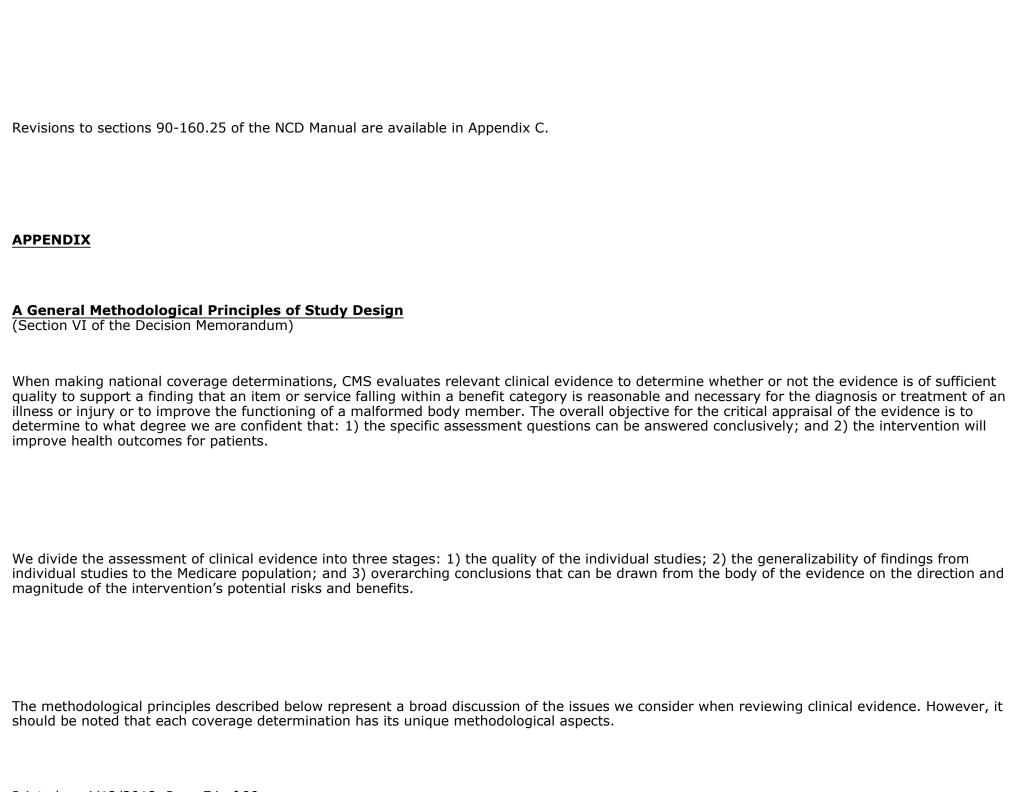
Prospectively, in Medicare beneficiaries with MDS who receive hematopoietic stem cell transplantation, what treatment facility characteristics predict meaningful clinical improvement in the following outcomes:

- relapse free mortality,
- progression free survival,
- o relapse, and
- overall survival?

The clinical study must adhere to the following standards of scientific integrity and relevance to the Medicare population:

- a. The principal purpose of the research study is to test whether a particular intervention potentially improves the participants' health outcomes.
- b. The research study is well supported by available scientific and medical information or it is intended to clarify or establish the health outcomes of interventions already in common clinical use.
- c. The research study does not unjustifiably duplicate existing studies.
- d. The research study design is appropriate to answer the research question being asked in the study.
- e. The research study is sponsored by an organization or individual capable of executing the proposed study successfully.
- f. The research study is in compliance with all applicable Federal regulations concerning the protection of human subjects found at 45 CFR Part 46. If a study is regulated by the Food and Drug Administration (FDA), it must be in compliance with 21 CFR parts 50 and 56.
- g. All aspects of the research study are conducted according to appropriate standards of scientific integrity (see <a href="http://www.icmje.org">http://www.icmje.org</a>).
- h. The research study has a written protocol that clearly addresses, or incorporates by reference, the standards listed here as Medicare requirements for CED coverage.
- i. The clinical research study is not designed to exclusively test toxicity or disease pathophysiology in healthy individuals. Trials of all medical technologies measuring therapeutic outcomes as one of the objectives meet this standard only if the disease or condition being studied is life threatening as defined in 21 CFR § 312.81(a) and the patient has no other viable treatment options.
- j. The clinical research study is registered on the ClinicalTrials.gov website by the principal sponsor/investigator prior to the enrollment of the first study subject.
- k. The research study protocol specifies the method and timing of public release of all prespecified outcomes to be measured including release of outcomes if outcomes are negative or study is terminated early. The results must be made public within 24 months of the end of data collection. If a report is planned to be published in a peer reviewed journal, then that initial release may be an abstract that meets the requirements of the International Committee of Medical Journal Editors (<a href="http://www.icmje.org">http://www.icmje.org</a>). However a full report of the outcomes must be made public no later than three (3) years after the end of data collection.
- I. The research study protocol must explicitly discuss subpopulations affected by the treatment under investigation, particularly traditionally underrepresented groups in clinical studies, how the inclusion and exclusion criteria effect enrollment of these populations, and a plan for the retention and reporting of said populations on the trial. If the inclusion and exclusion criteria are expected to have a negative effect on the recruitment or retention of underrepresented populations, the protocol must discuss why these criteria are necessary.
- m. The research study protocol explicitly discusses how the results are or are not expected to be generalizable to the Medicare population to infer whether Medicare patients may benefit from the intervention. Separate discussions in the protocol may be necessary for populations eligible for Medicare due to age, disability or Medicaid eligibility.

Consistent with section 1142 of the Social Security Act, AHRQ supports clinical research studies that CMS determines meet the above-listed standards and address the above-listed research questions.



#### **Assessing Individual Studies**

Methodologists have developed criteria to determine weaknesses and strengths of clinical research. Strength of evidence generally refers to: 1) the scientific validity underlying study findings regarding causal relationships between health care interventions and health outcomes; and 2) the reduction of bias. In general, some of the methodological attributes associated with stronger evidence include those listed below:

- Use of randomization (allocation of patients to either intervention or control group) in order to minimize bias.
- Use of contemporaneous control groups (rather than historical controls) in order to ensure comparability between the intervention and control groups.
- Prospective (rather than retrospective) studies to ensure a more thorough and systematical assessment of factors related to outcomes.
- Larger sample sizes in studies to help ensure adequate numbers of patients are enrolled to demonstrate both statistically significant as well as clinically significant outcomes that can be extrapolated to the Medicare population. Sample size should be large enough to make chance an unlikely explanation for what was found.
- Masking (blinding) to ensure patients and investigators do not know to which group patients were assigned (intervention or control). This is important especially in subjective outcomes, such as pain or quality of life, where enthusiasm and psychological factors may lead to an improved perceived outcome by either the patient or assessor.

Regardless of whether the design of a study is a randomized controlled trial, a non-randomized controlled trial, a cohort study or a case-control study, the primary criterion for methodological strength or quality is the extent to which differences between intervention and control groups can be attributed to the intervention studied. This is known as internal validity. Various types of bias can undermine internal validity. These include:

- Different characteristics between patients participating and those theoretically eligible for study but not participating (selection bias).
- Co-interventions or provision of care apart from the intervention under evaluation (performance bias).
- Differential assessment of outcome (detection bias).
- Occurrence and reporting of patients who do not complete the study (attrition bias).

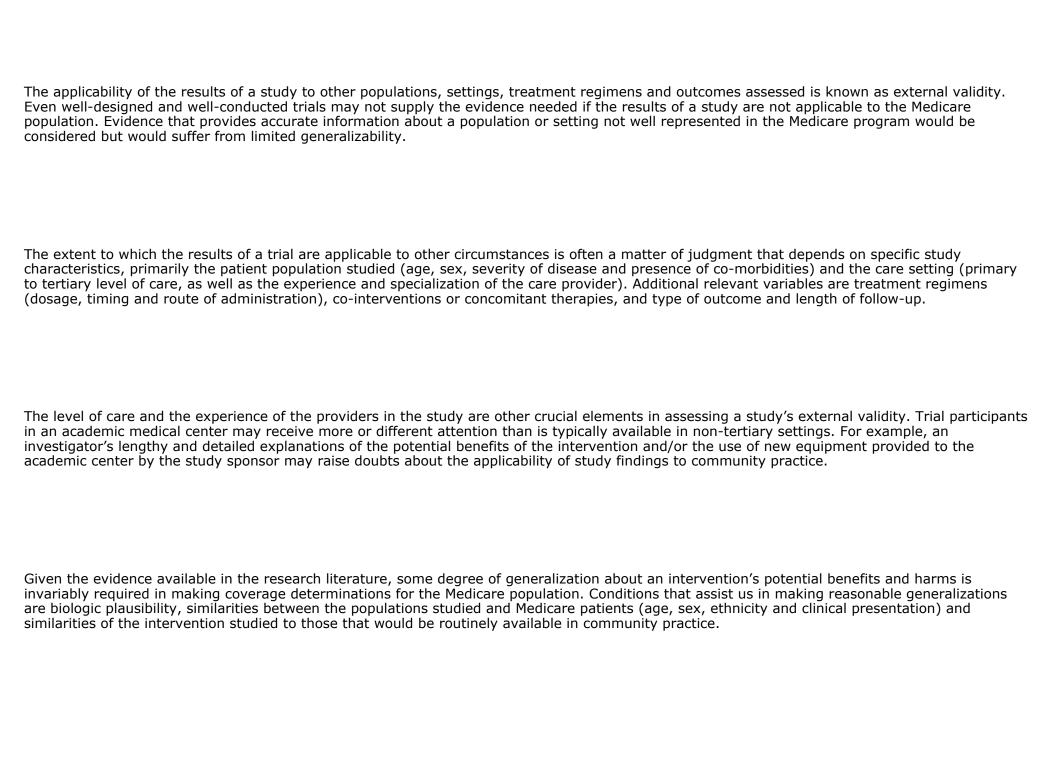
In principle, rankings of research design have been based on the ability of each study design category to minimize these biases. A randomized controlled trial minimizes systematic bias (in theory) by selecting a sample of participants from a particular population and allocating them randomly to the intervention and control groups. Thus, in general, randomized controlled studies have been typically assigned the greatest strength, followed by non-randomized clinical trials and controlled observational studies. The design, conduct and analysis of trials are important factors as well. For example, a well designed and conducted observational study with a large sample size may provide stronger evidence than a poorly designed and conducted randomized controlled trial with a small sample size. The following is a representative list of study designs (some of which have alternative names) ranked from most to least methodologically rigorous in their potential ability to minimize systematic bias:

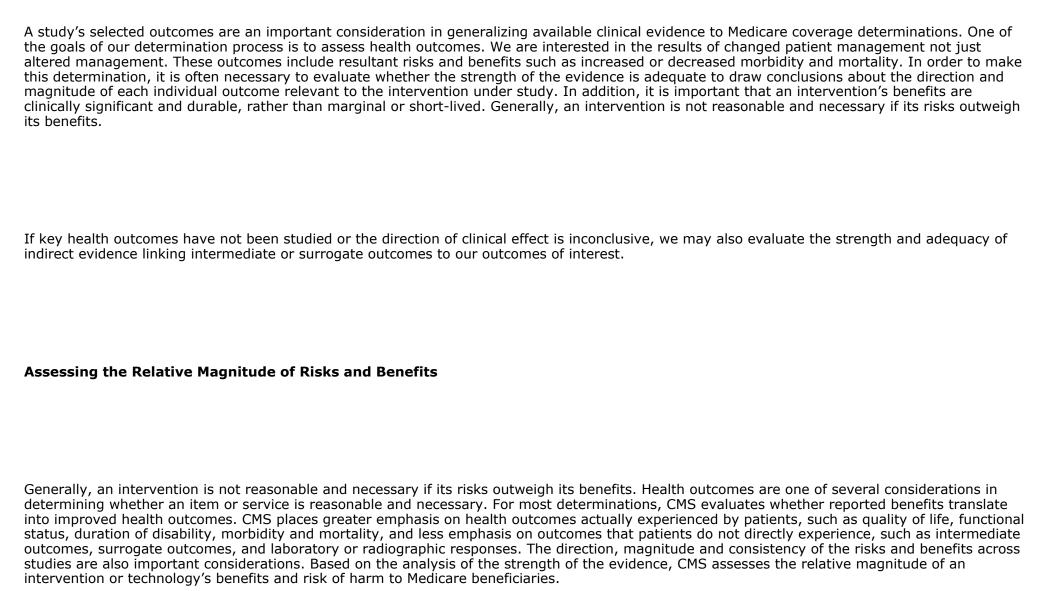
- Randomized controlled trials
- Non-randomized controlled trials
- Prospective cohort studies
- Retrospective case control studies
- Cross-sectional studies
- Surveillance studies (e.g., using registries or surveys)
- Consecutive case series
- Single case reports

When there are merely associations but not causal relationships between a study's variables and outcomes, it is important not to draw causal inferences. Confounding refers to independent variables that systematically vary with the causal variable. This distorts measurement of the outcome of interest because its effect size is mixed with the effects of other extraneous factors. For observational, and in some cases randomized controlled trials, the method in which confounding factors are handled (either through stratification or appropriate statistical modeling) are of particular concern. For example, in order to interpret and generalize conclusions to our population of Medicare patients, it may be necessary for studies to match or stratify their intervention and control groups by patient age or co-morbidities.

Methodological strength is, therefore, a multidimensional concept that relates to the design, implementation and analysis of a clinical study. In addition, thorough documentation of the conduct of the research, particularly study selection criteria, rate of attrition and process for data collection, is essential for CMS to adequately assess and consider the evidence.

**Generalizability of Clinical Evidence to the Medicare Population** 

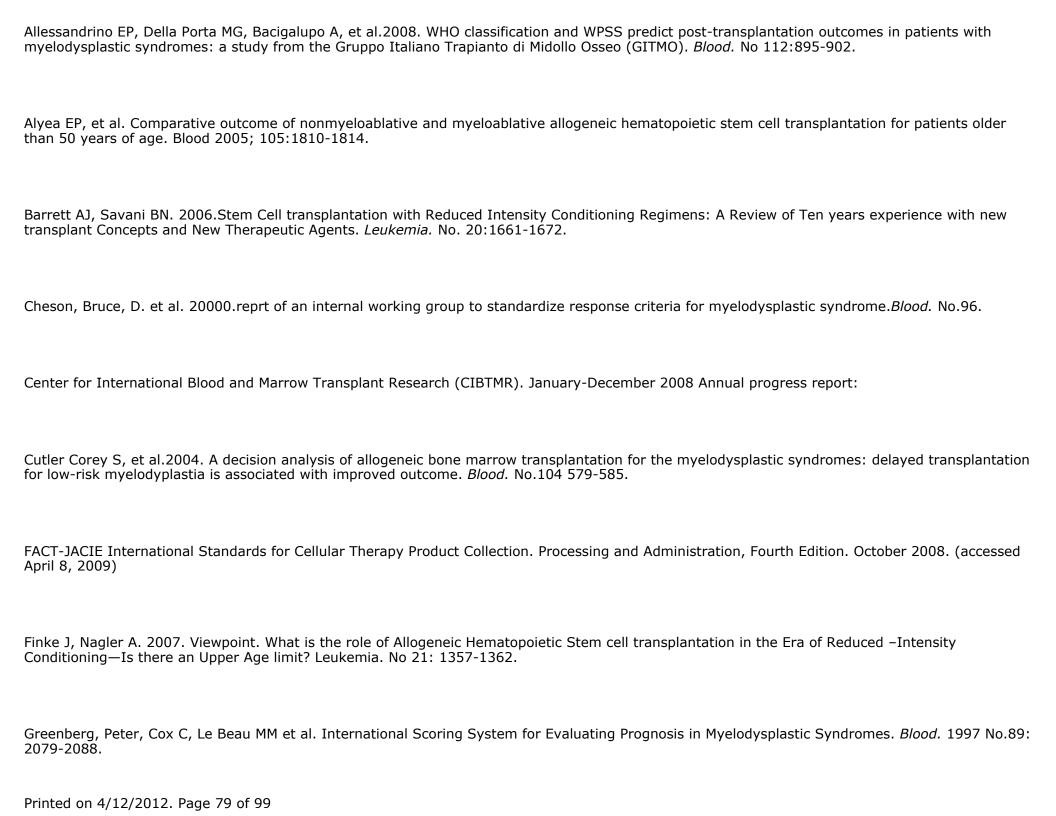


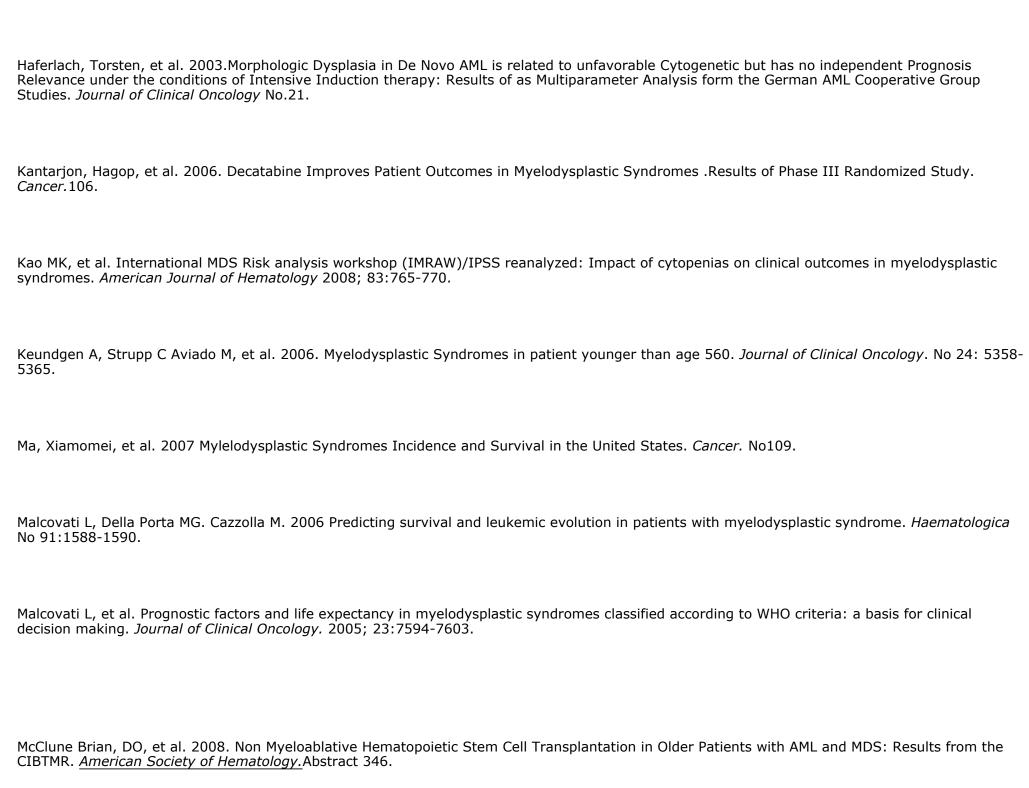


Appendix B

## **Reference Articles Submitted by Requestors**

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McClune Brian, DO, et al. Effect of Age on Outcomes of Non Myeloablative Hematopoietic Stem Cell Transplantation in Older Patients with AML in First Complete Remission and + MDS. Draft Manuscript.
National Comprehensive Cancer network (NCCN) Clinical Practice Guidelines in Oncology. Myelosdysplastic Syndromes, V.2.2010.Released August 26, 2009. <a href="https://www.nccn.org">www.nccn.org</a> (free but registration required) Accessed December 15, 2009. Nimer S. et al, 2008. Myelodysplastic Syndromes. <i>Blood</i> No.111:4841-51.
Nimer, S, et al. 2008. Melodysplastic Syndromes. <i>Blood.</i> No.111:4841-51.
NMDP 20 <sup>th</sup> Edition Standard and Glossary. March 30, 2009. (accessed April 8, 2009)
NMDP Transplant Center Participation criteria. February 2009 (accessed April 8, 2009).
Oliansky D, et al 2009. The Role of Cytotoxic Therapy with hematopoietic stem cell transplantation in the therapy of MDS: An Evidence Based-review. Biology of Blood and Bone Marrow Transplantation. No.15:137-172.
Plesa, Claudiu, ET al.2008. Prognostic Index for Older Adult patients with Newly Diagnosed Acute Myeloid Leukemia. The Edouard Herriot Hospital experience. Clinical leukemia. No.3.

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Rollison DE, Howlader N. Smith MT, et al. 2008. Epidemiology of myelodysplastic syndromes and chronic myeloproliferative disorders in the United States. 2001-2004. Blood No.112:45-52.
Silverman, Lewis, et al. 2006. Further Analysis of trials with Azacitidien in patients with Myelodysplastic Syndrome; Studies 8421, 8921and 9221 by the Cancer and Leukemia Group B. <i>Journal of Clinical Oncology</i> . No.24 (August 20).
Sorror ML, Sandmaier BM, Storer BE, et al. 2007. Co-morbidity and disease status based risk stratification of outcomes among patients with acute myeloid leukemia or myelodysplasia receiving allogeneic hematopoietic cell transplantation. <i>Journal of Clinical Oncology</i> . No. 25-4246-4254.
Sypridonidis A, Bertz H.2005. Hematopoietic Cell Transplantation from unrelated donors as an effective therapy for older patients. (>60 years) with Active Myeloid Malignancies. <i>Blood.</i> No .105:4147-4148.
Vardiman JW, Harris NL,Brunning RD 2002. The World Health Organization (WHO) Classification of the myeloid neoplasm. <i>Blood</i> . No 100:2292-302.
Appendix C
DRAFT

## **Medicare National Coverage Determinations Manual**

# **Chapter 1, Part 2 (Section 110.8.1.)**

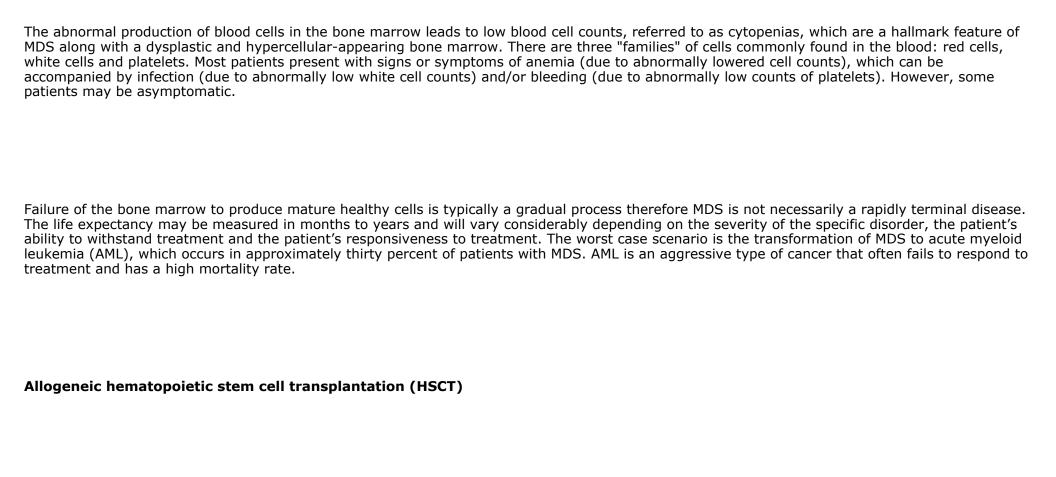
## **Coverage Determinations Table of Contents** (Rev.)

xxx. - Allogeneic Hematopoietic Stem Cell Transplantation for Myelodysplastic Syndromes (Effective xx, xx, 2010)

Xxx.xx- Allogeneic Hematopoietic Stem Cell Transplantation for Myelodysplastic Syndromes (Effective xx,xx, 2010) (Rev.)

#### A. General

Myelodysplastic Syndrome (MDS) refers to a group of diverse blood disorders in which the bone marrow does not produce enough healthy, functioning blood cells. These bone marrow disorders are varied with regard to clinical characteristics, cytologic and pathologic features, and cytogenetics.



Hematopoietic stem cells are multipotent stem cells that give rise to all the blood cell types; these stem cells form blood and immune cells. A hematopoietic stem cell is a cell isolated from blood or bone marrow that can renew itself, differentiate to a variety of specialized cells, can mobilize out of the bone marrow into circulating blood, and can undergo programmed cell death, called apoptosis—a process by which cells that are unneeded or detrimental self destruct. Stem cell transplantation is a process in which stem cells come from either a patient's (autologous) or donor's (allogeneic) peripheral blood for intravenous infusion. Autologous Transplant patients receive their own stem cells. Allogeneic transplant patients receive stem cells from a parent or sibling, or unrelated donor. Allogeneic stem cell transplantation is a procedure in which a portion of a healthy donor's stem cell or bone marrow is obtained and prepared for intravenous infusion. Allogeneic HSCT is commonly used in cancer treatment in conjunction with very high doses of chemotherapy and/or radiation therapy to make the chemotherapy regimen possible.

#### **B.** Conclusion

CMS determines that the evidence does not demonstrate that the use of allogeneic HSCT improves health outcomes in Medicare beneficiaries with MDS. Therefore, we determine that allogeneic HSCT for MDS is not reasonable and necessary under §1862(a) (1) (A) of the Social Security Act. However, we do believe the available evidence suggests that allogeneic HSCT for MDS has the potential to improve health outcomes and supports additional research for this treatment under §1862(a) (1) (E) of the Social Security Act through Coverage with Evidence Development (CED). Therefore, HSCT for MDS will be covered by Medicare under Coverage with Evidence Development (CED) as reasonable and necessary when beneficiaries are enrolled in a clinical study that meets all of the criteria listed below. The intent of studies developed to fulfill the CED requirements is to generate evidence of the health benefit of allogeneic HSCT for MDS.

"Allogeneic HSCT is covered for beneficiaries who have MDS who are candidates for this procedure pursuant to CED in the context of an approved clinical study.

Medicare payment for these beneficiaries will be restricted to patients enrolled in a prospective clinical study. In accordance with the Stem Cell Therapeutic and Research Act of 2005 (US Public Law 109-129) a standard dataset is collected for all allogeneic transplant patients in the United States by the CIBTMR. The elements in this dataset, comprised of 2 mandatory forms plus one additional form, encompass the information we require for a study under CED.

Allogeneic hematopoietic stem cell transplantation for myelodysplastic syndromes is covered by Medicare only in the context of a prospective clinical study. Payment will be made only for patients with MDS participating in an approved controlled clinical study with design characteristics described below.

A clinical study seeking Medicare payment for allogeneic hematopoietic stem cell transplantation for myelodysplastic syndrome pursuant to Coverage with Evidence Development (CED) must address one or more aspects of the following questions.

Prospectively, compared to Medicare beneficiaries with MDS who do not receive hematopoietic stem cell transplantation, do Medicare beneficiaries with MDS who receive hematopoietic stem cell transplantation have improved outcomes as indicated by:

relapse free mortality,

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- progression free survival,
- relapse, and
- overall survival?

Prospectively, in Medicare beneficiaries with MDS who receive hematopoietic stem cell transplantation, how do International Prognostic Scoring System (IPSS) score, patient age, cytopenias and comorbidities predict the following outcomes:

- relapse free mortality,
- progression free survival,
- relapse, and
- overall survival?

Prospectively, in Medicare beneficiaries with MDS who receive hematopoietic stem cell transplantation, what treatment facility characteristics predict meaningful clinical improvement in the following outcomes:

- relapse free mortality,
- progression free survival,
- relapse, and
- overall survival?

The clinical study must adhere to the following standards of scientific integrity and relevance to the Medicare population:

- 1. The principal purpose of the research study is to test whether a particular intervention potentially improves the participants' health outcomes.
- 2. The research study is well supported by available scientific and medical information or it is intended to clarify or establish the health outcomes of interventions already in common clinical use.
- 3. The research study does not unjustifiably duplicate existing studies.
- 4. The research study design is appropriate to answer the research question being asked in the study.
- 5. The research study is sponsored by an organization or individual capable of executing the proposed study successfully.
- 6. The research study is in compliance with all applicable Federal regulations concerning the protection of human subjects found at 45 CFR Part 46. If a study is regulated by the Food and Drug Administration (FDA), it must be in compliance with 21 CFR parts 50 and 56.
- 7. All aspects of the research study are conducted according to appropriate standards of scientific integrity (see <a href="http://www.icmje.org">http://www.icmje.org</a>).

- 8. The research study has a written protocol that clearly addresses, or incorporates by reference, the standards listed here as Medicare requirements for CED coverage.
- 9. The clinical research study is not designed to exclusively test toxicity or disease pathophysiology in healthy individuals. Trials of all medical technologies measuring therapeutic outcomes as one of the objectives meet this standard only if the disease or condition being studied is life threatening as defined in 21 CFR § 312.81(a) and the patient has no other viable treatment options.
- 10. The clinical research study is registered on the ClinicalTrials.gov website by the principal sponsor/investigator prior to the enrollment of the first study subject.
- 11. The research study protocol specifies the method and timing of public release of all prespecified outcomes to be measured including release of outcomes if outcomes are negative or study is terminated early. The results must be made public within 24 months of the end of data collection. If a report is planned to be published in a peer reviewed journal, then that initial release may be an abstract that meets the requirements of the International Committee of Medical Journal Editors (<a href="http://www.icmje.org">http://www.icmje.org</a>). However a full report of the outcomes must be made public no later than three (3) years after the end of data collection.
- 12. The research study protocol must explicitly discuss subpopulations affected by the treatment under investigation, particularly traditionally underrepresented groups in clinical studies, how the inclusion and exclusion criteria effect enrollment of these populations, and a plan for the retention and reporting of said populations on the trial. If the inclusion and exclusion criteria are expected to have a negative effect on the recruitment or retention of underrepresented populations, the protocol must discuss why these criteria are necessary.
- 13. The research study protocol explicitly discusses how the results are or are not expected to be generalizable to the Medicare population to infer whether Medicare patients may benefit from the intervention. Separate discussions in the protocol may be necessary for populations eligible for Medicare due to age, disability or Medicaid eligibility.

Consistent with section 1142 of the Social Security Act, AHRQ supports clinical research studies that CMS determines meet the above-listed standards and address the above-listed research questions.

The clinical research study must adhere to the following standards of scientific integrity and relevance to the Medicare population. The clinical research study should have the following features:

- It should be a comparative prospective longitudinal study with clinical information from the period before HSCT and short and long term follow up information.
- Outcomes should be measured and compared among pre-specified subgroups within the cohort.
- The study should be powered to make inferences in subgroup analyses.
- Risk stratification methods should be used to control for selection bias. Data elements to be used in risk stratification models should include:

#### **Patient selection:**

Risk stratification methods should be used to control for selection bias. Data elements to be used in risk stratification models should include:

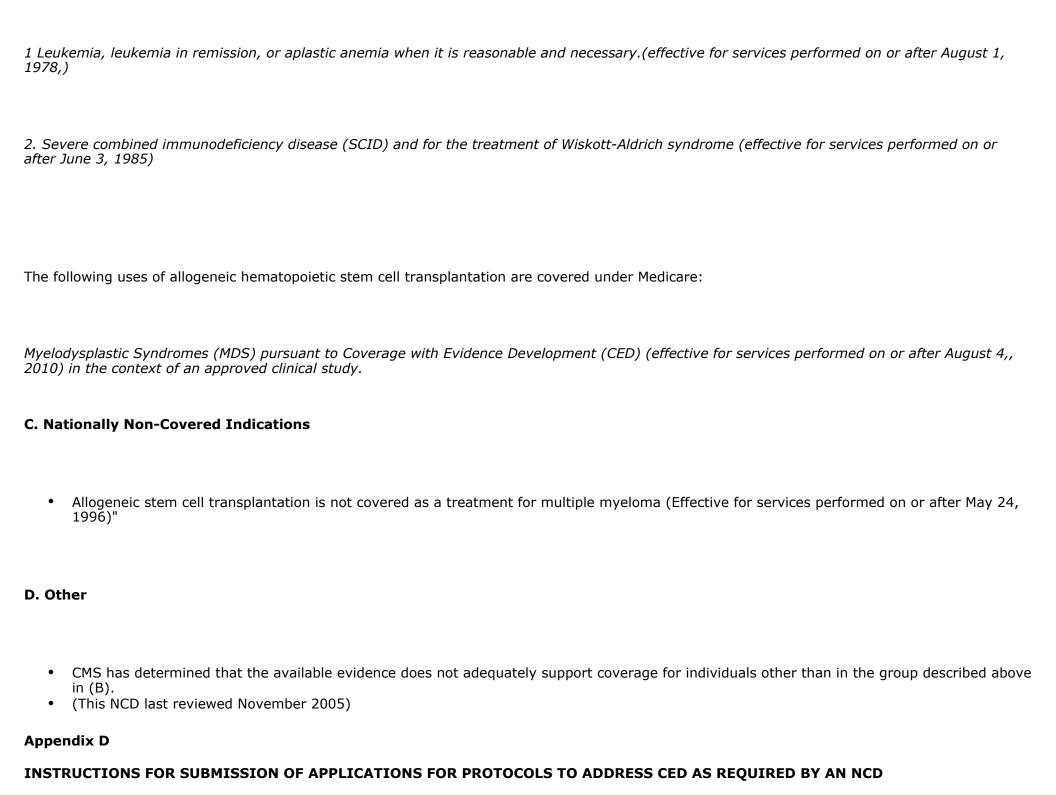
- Patient Age at diagnosis of MDS and at transplantation
- Date of onset of MDS
- Disease classification (specific MDS subtype at diagnosis prior to preparative /conditioning regimen using WHO classification). Include presence/absence of refractory cytopenias.
- · Co morbid conditions
- IPSS score (and WPSS score, if applicable) at diagnosis and prior to transplantation
- Score immediately prior to transplantation and one year post transplantation
- Disease assessment at diagnosis at start of preparative regimen and last assessment prior to preparative regimen Subtype of MDS (refractory anemia with or without blasts, degree of blasts, etc.)
- Type of preparative/conditioning regimen administered (myeloabalative, non-myeloablative, reduced -intensity conditioning)
- Donor type
- Cell Source
- IPSS Score at diagnosis

## **Facility Criteria**

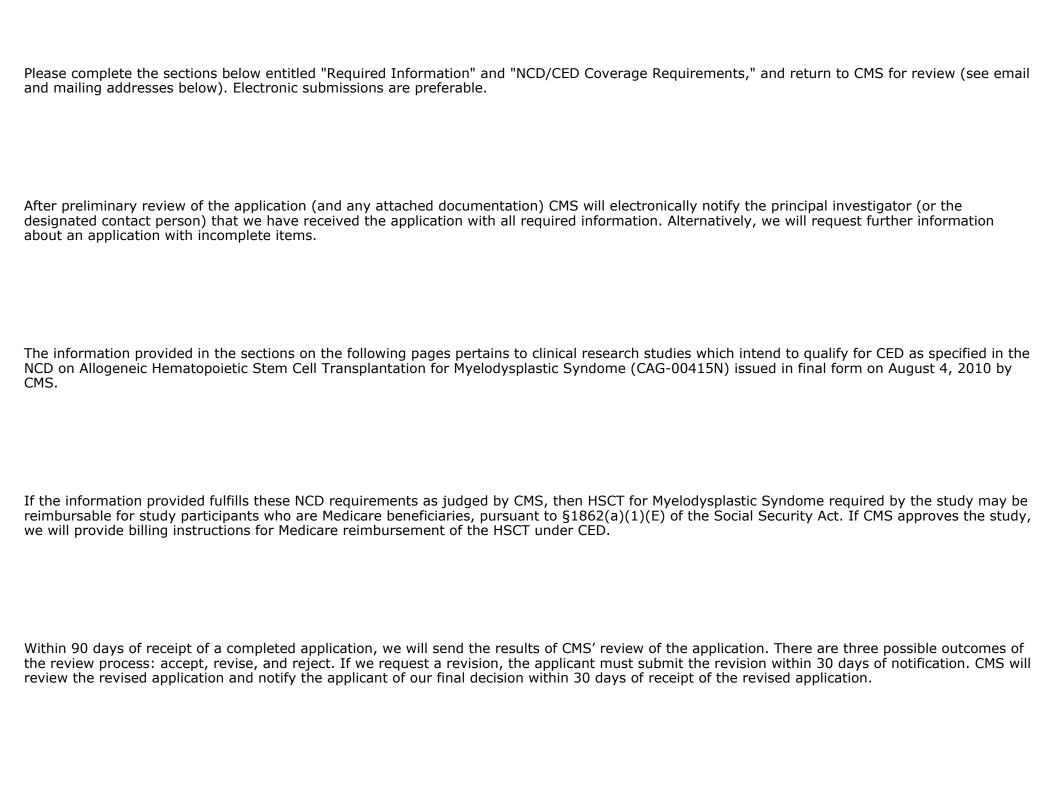
• Facilities must submit the required transplant essential data to the SCTOD.

## **B. Nationally Covered Indications**

The following uses of allogeneic bone marrow transplantation are covered under Medicare:



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#### **REQUIRED INFORMATION**

- 1. Date of submission
- 2. **Descriptive title**
- 3. Contact information:
  - Name and title of principal investigator (PI)
  - Name and title of contact person if other than the PI
  - o PI's (or contact person's) mailing address, telephone number, fax, and email address
  - o Institutional or organizational affiliation
  - Study sponsor(s)
- 4. Brief annual updates or websites that CMS may access to get the information below:

Please send updates electronically to leslye.fitterman3@cms.hhs.gov (or the mailing address below) that contain the following information about Medicare patients enrolled in the study:

- Number screened
- Number enrolled
- Reason for non-enrollment
- Number of dropouts
- Reason for dropout
- o Number with completed data collection
- Progress of data analysis
  - Analysis file constructed (y/n)
  - Analyses to address each hypothesis completed (y/n)
- Manuscript completed (y/n)
- Manuscript sent to journal (date)

### NCD/CED COVERAGE REQUIREMENTS

CMS	will review and evaluate the protocol to ensure that the proposed study protocol meets the following requirements.
1.	Study population: qualifications for study
	The protocol should describe the criteria for Medicare beneficiaries to be included and excluded from the study.
2.	Evaluation of outcomes
	The protocol should define each outcome to be studied and explain method(s) and timing(s) of outcome assessment(s). The description should include expected length of follow up for participants. The study sample size and duration should allow for reliable estimate(s) of all outcome endpoints.
	At minimum, the outcomes to be studied must include one of the following for the study to be eligible for coverage:
	<ul> <li>relapse free mortality,</li> <li>progression free survival,</li> <li>relapse, and</li> <li>overall survival?</li> </ul>
3.	Standards of scientific integrity and relevance to the Medicare population

Note: Please include a specific reference to the page or pages in your application with your response to the following.

a.

The principal purpose of the research study is to test whether a particular intervention potentially improves the participants' health outcomes.

Describe how you will measure the outcomes listed in the NCD.

b.

The research study is well-supported by available scientific and medical information or it is intended to clarify or establish the health outcomes of interventions already in common clinical use.

- Provide a brief review of pertinent published research that support your study hypotheses and methods.
- c. The research study does not unjustifiably duplicate existing studies.
  - Justify that your study adds to existing evidence.

d.

The research study design is appropriate to answer the research question being asked in the study.

The response to this Standard should contain the following:

- Introduction
- Hypotheses to be tested
- Specific aims
- Background and significance
- Trial design
- Target population and recruitment target
- Inclusion/exclusion criteria
- Power calculations
  - a. Effect size
  - b. Basis of selected effect size

The research study must meet one or more aspects of the following questions:

1.

Prospectively, compared to Medicare beneficiaries with MDS who do not receive hematopoietic stem cell transplantation, do Medicare beneficiaries with MDS who receive hematopoietic stem cell transplantation have improved outcomes as indicated by:

- relapse free mortality,
- progression free survival,
- relapse, and
- overall survival?

2.

Prospectively, in Medicare beneficiaries with MDS who receive hematopoietic stem cell transplantation, how do International Prognostic Scoring System (IPSS) score, patient age, cytopenias and comorbidities predict the following outcomes:

- relapse free mortality,
- progression free survival,
- relapse, and
- overall survival?

3.

Prospectively, in Medicare beneficiaries with MDS who receive hematopoietic stem cell transplantation, what treatment facility characteristics predict meaningful clinical improvement in the following outcomes:

- relapse free mortality,
- progression free survival,
- relapse, and
- overall survival?

e.

The research study is sponsored by an organization or individual capable of executing the proposed study successfully.

- Provide CVs of investigators with a description of their contribution to the project.
- Describe the capabilities of the study sites.

f.	The research study is in compliance with all applicable Federal regulations concerning the protection of human subjects found in the Code of Federal Regulations (CFR) at 45 CFR Part 46. If a study is regulated by the Food and Drug Administration (FDA), it also must be in compliance with 21 CFR Parts 50 and 56.  • Provide IRB approval letters from an IRB that is in compliance with 21 CFR Parts 50 and 56 for each site. Approvals should be
	updated before study initiation at each site. (Sites will be listed on the CMS website.)
g.	All aspects of the research study are conducted according to the appropriate standards of scientific integrity. <ul> <li>Describe data safety monitoring procedures.</li> <li>Describe stopping rules.</li> </ul>
h.	
	The research study has a written protocol that clearly addresses, or incorporates by reference, the Medicare standards.
	Required of all CED projects.
i.	
	The clinical research study is not designed to exclusively test toxicity or disease pathophysiology in healthy individuals. Trials of all medical technologies measuring therapeutic outcomes as one of the objectives meet this standard only if the disease or condition being studied is life-threatening as defined in 21 CFR § 312.81(a) and the patient has no other viable treatment options.
	Note: this standard is not relevant to this NCD. No answer required.
j.	

The clinical research study is registered on the www.ClinicalTrials.gov website by the principal sponsor/investigator prior to the enrollment of the first study subject.

Plans to register the study if approved by CMS should be stated. (The ClinicalTrials.gov identifier is required for payment for HSCT)

k.

The research study protocol specifies the method and timing of public release of all pre-specified outcomes to be measured including release of outcomes if outcomes are negative or study is terminated early. The results must be made public within 24 months of the end of data collection. If a report is planned to be published in a peer-reviewed journal, then that initial release may be an abstract that meets the requirements of the International Committee of Medical Journal Editors. However, a full report of the outcomes must be made public no later than three (3) years after the end of data collection.

•

Describe your approach to dissemination of the study results.

١.

The research study protocol must explicitly discuss subpopulations affected by the treatment under investigation, particularly traditionally underrepresented groups in clinical studies, how the inclusion and exclusion criteria affect enrollment of these populations, and a plan for the retention and reporting of said populations on the trial. If the inclusion and exclusion criteria are expected to have a negative effect on the recruitment or retention of underrepresented populations, the protocol must discuss why these criteria are necessary. Address the following:

- Inclusion and exclusion criteria and how they will affect enrollment.
- Inclusion of women and minorities.
- Inclusion of Medicare enrollees.

m.

The research study protocol explicitly discusses how the results are or are not expected to be generalizable to the Medicare population to infer whether Medicare patients may benefit from the intervention. Separate discussions in the protocol may be necessary for populations eligible for Medicare due to age, disability or Medicaid eligibility.

Discuss how the methodology addresses the above issues.

Submit the "Required Information," "NCD/CED Coverage Requirements," and study protocol to: <a href="mailto:Leslye.fitterman3@cms.hhs.gov">Leslye.fitterman3@cms.hhs.gov</a> or

Leslye Fitterman, PhD. 7500 Security Boulevard Mail Stop C1-09-06 Baltimore, MD 21244-1850 Back to Top

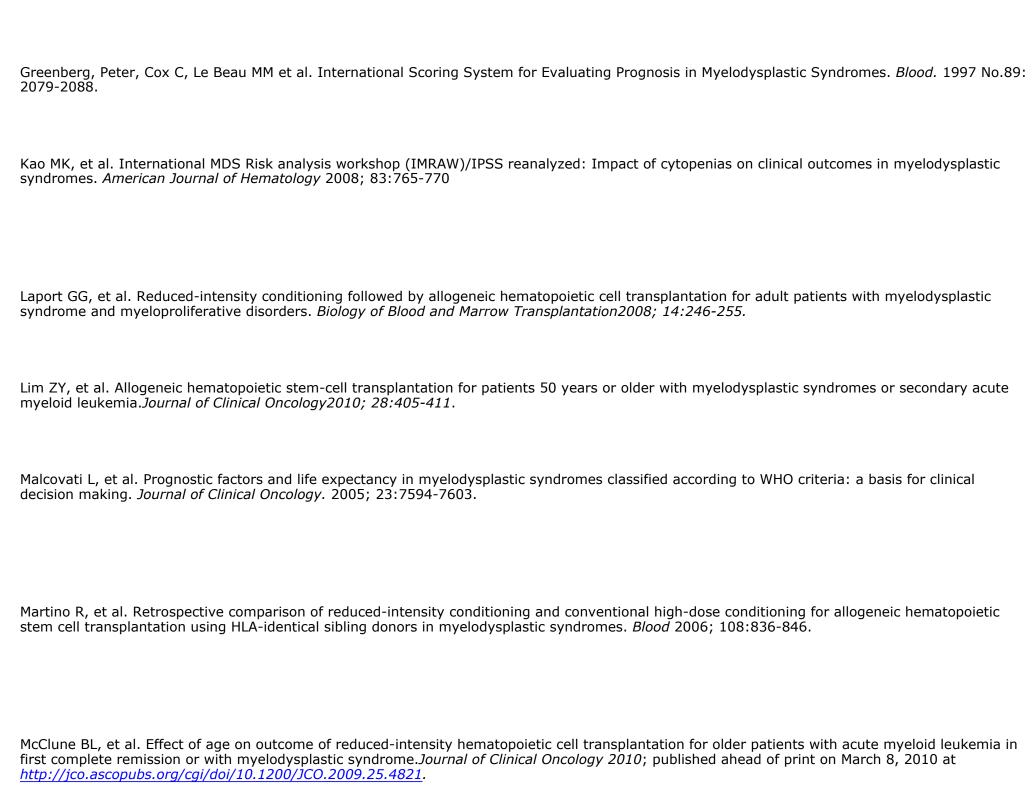
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